REVIEW ARTICLE

Current Understanding of the Neurobiology of Pain

Yu KS, Chan PT
Department of Orthopaedics and Traumatology, North District Hospital, Hong Kong

ABSTRACT

Pain is a complex and poorly understood phenomenon. Recent advances through clinical experience and experimental studies have revealed that afferent information does not become consciously known as pain through any simple or easily defined chains of neurones. There is also increasing scientific evidence showing that both short-term and long-term changes do occur within the peripheral and central nervous system following noxious input. This paper highlights the plasticity phenomenon in the pain system to facilitate our understanding of pain and hence the principles behind some of the more recent pain management concepts.

Key Words: Neurobiology, Pain, Pathophysiology, Physiological pain

INTRODUCTION

Ethel Mumford (1878-1940), an American writer and dramatist wrote, “knowledge is power if you know it”. However, it is not uncommon to find out that descriptions of the pain system in classical orthopaedic textbooks are far from complete. Back pain, neck pain, fibromyalgia, phantom limb pain, and complex regional pain syndrome are some pain conditions that orthopaedic surgeons have to deal with nowadays. It can be frustrating not knowing what help or advice to offer when all the ‘standard treatments’ have had no effect for patients with persistent pain.

There is increasing scientific evidence that both short-term and long-term changes occur within the peripheral and central nervous system following noxious input. This plasticity phenomenon of the nervous system then alters the body’s response to further peripheral sensory input. This paper highlights the plasticity phenomenon in the pain system to facilitate understanding of pain and hence the principles behind some of the more recent pain management concepts.

PHYSIOLOGICAL AND PATHOPHYSIOLOGICAL PAIN

In normal conditions, low intensity, non-noxious stimuli activate low-threshold receptors to generate innocuous sensations. On the other hand, high intensity, noxious stimuli activate high-threshold receptors, which are encoded in the periphery, propagated centrally, processed, and then perceived as pain. This is termed as physiological pain (Figure 1a).

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on the intensity, location, and dynamics of strong tissue-threatening stimuli. This permits individuals to avoid harm. While retaining this basic layout, there is increasing evidence that powerful modulatory mechanisms exist in the nervous system. Abnormal and chronic pain states are better understood in terms of the functioning of these modulatory processes.3 There are central and peripheral changes leading to abnormal excitability in the nervous system. Indeed, insult to the body that produces pain also causes nerve injury, tissue damage, and inflammatory changes, which directly or indirectly affect the response of receptors to further stimulation. This type of pain is termed as pathophysiological or clinical pain (Figure 1b).1,2 Any individual patient may show symptoms and signs of either or both types of pain. The respective special features are listed in Table 1.

**NORMAL PAIN PATHWAY**

First of all, in what way are the sensory signals initially generated in skin, muscle, and tendon? Most investigators agree that receptors mediating pain, called nociceptors, can be distinguished from other receptors as a distinct group. Being the least differentiated sensory receptors, these nociceptors are pseudo-unipolar sensory neurons and have free nerve endings. They are activated by potentially tissue-damaging stimuli applied to cutaneous or subcutaneous tissues. The free nerve endings contain several substances stored in vesicles such as substance P, bradykinins (BKs), and prostaglandins (PGs).

The working mechanism of nociceptors is not known, but one hypothesis is as follows. The substances are released in response to a particular stimulation. The released agent combines with the external surface of the nerve ending and causes it to depolarise. Action potentials are formed. The action potential is terminated by the appropriate enzyme. The nociceptors are capable of distinguishing between innocuous and noxious events, and of encoding in their discharge the intensity of the noxious stimulus.4

For the somatic structures relevant to orthopaedic surgeons, the skin is supplied by A-δ high-threshold mechanoreceptors (HTMs), A-δ myelinated mechano-thermal nociceptors (MMTNs), C polymodal nociceptors (CPNs) activated by mechanical, thermal, and chemical noxious stimuli, and by a miscellaneous group consisting of C mechanical nociceptors and cold nociceptors. Muscles, joints, fasciae, and other deep somatic structures are supplied by C and also probably by A-δ fibres (Figure 2).5,6

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**Table 1** Special features of physiological and pathophysiological pain.2 Reproduced with permission from Lippincott Williams and Wilkins.

<table>
<thead>
<tr>
<th>Physiological pain</th>
<th>Pathophysiological pain</th>
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<tbody>
<tr>
<td>• Pain (A-δ and C fibres) can be differentiated from touch (A-β fibres)</td>
<td>• Pain can be elicited by A-δ and C as well as A-β fibres</td>
</tr>
<tr>
<td>• Pain serves a protective function</td>
<td>• Pain is ‘pathological’, for example, it is associated with inflammation, neuropathy, and so on.</td>
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<tr>
<td>• Pain acts as a warning of potential damage</td>
<td>• Occurs in the context of peripheral sensitisation</td>
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<tr>
<td>• Pain is well localised</td>
<td>• Occurs in the context of central sensitisation</td>
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<tr>
<td>• Stimulus-response pattern is the same as other sensory modalities, for example, touch</td>
<td>• Outlasts the stimulus</td>
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<td>• Spreads to non-damaged areas</td>
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Nociceptors typically have a high stimulation threshold, requiring noxious intensities of stimulation for clear activation. These receptors do not respond to everyday stimuli such as weak pressure, muscle stretching or contraction, and joint movements within the physiological range.

Two classes of afferent nerve fibres are responsible for communicating nociceptive information, as follows:

- **A-δ** afferent fibres are small-diameter rapidly conducting myelinated nociceptive fibres that conduct thermal or mechanical information at the rate of 5 to 30 m/second. The pain ascribed to these fibres has been described as being of a sharp, pricking nature.
- **C** fibre afferent nociceptive neurones are small diameter slowly conducting unmyelinated polymodal receptors that are activated by a wide variety of high-intensity stimuli, such as mechanical, chemical, and thermal, at rate of 0.5 to 2 m/second.

**PERIPHERAL SENSITISATION**

The sensitivity of nociceptors is not constant. Nociceptive stimuli that produce tissue damage often cause an increased sensitivity to subsequent stimuli because of the enhanced responsiveness of the involved nociceptors. This painful phenomenon is termed hyperalgesia, meaning an increased response to a stimulus that is normally painful, and reflects an increased pain on suprathreshold stimulation.

Nociceptor sensitisation results from local tissue damage as well as the release of algogenic substances, known as tissue autocoids, from either damaged cells or circulating platelets, lymphocytes, macrophages, and mast cells. A neurogenic inflammatory response following nociceptive stimulation results in release of substance P, neurokinin A, and calcitonin gene-related peptide (CGRP) from peripheral terminals of nociceptive afferent fibres. Hence, there are combinations of inflammatory mediators including potassium, serotonin, bradykinin, substance P, histamine, cytokines, nitric oxide, and products from the cyclo-oxygenase and lipoxygenase pathways of arachidonic acid metabolism. These chemicals in turn act as a ‘sensitising soup’ and sensitise high-threshold nociceptors that result in the phenomenon of peripheral sensitisation (Figure 3). This makes them more prone to activation by weak touch or...
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Thermal stimuli and during movement, which would not normally cause pain. The effect of direct activation and sensitisation may be independent.³

By lowering the response threshold of nociceptive endings in inflamed tissue, peripheral sensitisation evokes both direct nociceptive barrage that is felt as ongoing pain (burning, stinging), and also touch-, movement-, and temperature-evoked pain. These findings offer an explanation for pain associated with movements, and tenderness of inflamed muscles or joints lasting some time after a noxious insult in clinical settings.

All this accounts for the phenomenon of primary hyperalgesia, which is an increased response to a stimulus at the original site of tissue damage.³,8 It is the design of the pain system and not a reflection of disease.³ Indeed, one advantage of the modulatory mechanism is to minimise the use of injured and fragile tissue, to avoid further harm occurring.

Central Sensitisation

nociceptive afferent fibres terminate in the dorsal horn of the spinal cord, where they form synapses and activate second-order neurones. The signals from sensory neurones are mediated by excitatory amino acids including glutamate (sharp, rapid signal) and neuropeptides, such as substance P (slow, dull signal). Information from these neurones ascends through different tracts, including spinothalamic, spinoreticular, and spinomesencephalic tracts, to various parts of the brainstem or brain (Figure 4).⁶

However, it has long been observed that there is an increased responsiveness to normally innocuous mechanical stimuli following injuries in a zone of uninjured tissue surrounding the site of injury. The phenomenon is called ‘secondary hyperalgesia’.³

An important historical debate centered on whether secondary hyperalgesia is due to nociceptors sensitivity

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Figure 4  Schematic showing some of the peripheral cells and factors that interact with nociceptors via specific membrane receptors. Afferent signals to the neurone come from the indicated cells, all of which are affected by efferent release of neuropeptides, excitatory amino acids (EAA), or both, and neurotransmitters from the neurones. Systemic hormones such as oestrogen (E) or glucocorticoids (G) regulate neural renal function via receptors in the soma cytoplasm. In the central nervous system, there are equally complex interactions with central neurones and glia as well as with descending control fibres.⁷ Reproduced with permission from Lippincott, Williams and Wilkins.

Abbreviations: BK = bradykinin; CK = cytokines; CNTF = ciliary neurotrophic factor; GDNF = glial-derived neurotrophic factor; H+ = protons; His = histamine; NE = norepinephrine; NGF nerve growth factor; NO = nitric oxide; OP = opioid peptides; PG prostaglandins; TNF = tumour necrosis factor; 5-HT = serotonin.
by diffusion of algogenic substances or by axon reflex activity or is due to altered processing of impulses entering the central nervous system (CNS) along low-threshold A-β touch afferents.\cite{10,11} Scientific findings show that there is no change in threshold to thermal stimuli\cite{1} and support the latter hypothesis.\cite{3} First, using cuff and anaesthetic procedures that selectively block A and C fibres, secondary hyperalgesia fades with A fibre conduction and only returns when A fibre conduction is restored. Second, the stimulus-response latency of touch-evoked pain corresponds to conduction at A-fibre velocity. Third, intraneural and transcutaneous electrical stimulation of A-β axons, bypassing their sensory endings, elicits pain in the zone of secondary hyperalgesia and in the zone of primary hyperalgesia but not in intact skin. Finally, recording experiments have failed to yield evidence of nociceptor sensitisation away from the area of obvious inflammation. The same type of evidence indicates that in many cases of neuropathy, allodynic pain is evoked by activity in A-β afferents. In summary, A-β-evoked pain appears to be due to central sensitisation triggered by C-fibre input generated alternatively by noxious stimulation of intact skin or deep tissue, stimulation of sensitised C nociceptors in inflamed tissue, or ectopic firing of C afferents at sites of nerve injury and associated dorsal root ganglion.\cite{3} In clinical settings, A-β afferents contribute to persistent pain even though inflammatory mediators do not directly affect them. Central sensitisation is really a response of the normal central nervous system to the development of inflammation peripherally.\cite{12} This activity-dependent form of CNS plasticity is termed ‘wind-up’. Hence, clinical pain associated with nociceptive input is not a simple stimulus-response relationship, but a wind-up of spinal cord neuronal activity. It is this spinal hyperexcitability state that permits A-β touch-evoked input to be felt as pain, a form of mechanical allodynia. The wind-up process is dependent on activation of the N-methyl D-aspartate (NMDA) receptor.\cite{1} The NMDA receptor is one of the 3 receptors for L-glutamate, an Australian invention, being first synthesised and tested in Canberra at the Australian National University.\cite{12}

Central sensitisation can apparently be sustained indefinitely if the noxious conditioning input is maintained, as in chronic inflammatory diseases or in sustained ectopic firing in neuropathy. Secondary hyperalgesia is a dynamic phenomenon, and fades away when the noxious stimulus that triggers it ceases.\cite{13} For this reason, the primary noxious focus is said to both trigger and maintain central sensitisation.\cite{3}

There are 2 important aspects for pain management. First, there is the potential for the development of clinically suitable NMDA receptor antagonists for pain control. This is because a key aspect of the central sensitisation mechanism is the involvement of this receptor. Second, the demonstrations of the phenomenon of wind-up has a major impact on the concept of pain management. Examples include the search for pre-emptive analgesia. The idea is to prevent changes associated with wind-up by abolishing or reducing acute pain. One practical approach is to prevent the central sensitising effects of noxious input during surgery by supplementing general anaesthetics with regional anaesthetic block or with systemic opiates.\cite{14} McQuay showed that regional and spinal use of local anaesthetics in patients undergoing elective orthopaedic surgery significantly lengthened the pain-free period after surgery from under 2 hours to more than 8 hours.\cite{15} Patients who had pre-emptive block received less opiate analgesia postoperatively.

Both the peripheral and central sensitisation brings about sensory amplification and usually occurs together.\cite{16} However, one important difference is that peripheral sensitisation acts almost exclusively on nociceptor endings in peripheral tissue. Peripheral sensitisation simply renders them more responsive. Central sensitisation amplifies not only the signal of nociceptors, but also the signal of low-threshold A-β sensory fibres. This causes A-β touch input to be felt as pain.\cite{16}

**LONG-TERM CENTRAL NERVOUS SYSTEM PLASTICITY**

How can we account for a range of persistent and sometimes bizarre pain phenomena seen in the clinical setting? There is a belief that persistent pain can burn its way into CNS, becoming independent of peripheral input and nearly impossible to treat. The process is called centralisation.\cite{16} In fact, injury to peripheral nerves triggers a spectrum of long-term changes in central somatosensory circuitry that are not in any obvious way related to the nociceptor-driven central sensitisation mechanism just discussed. The development of chronic pain may have more to do with the phenomenon of long-term potentiation than it does with wind-up.\cite{12}

There is evidence that peripheral injury and injury-related sensory signals can alter gene expression in CNS neurones. This is also dependent on activation of NMDA receptors, and LTP3 in particular, which has a
longer time constant of approximately 30 days, and is associated with the induction of immediate early genes including fos-related genes. Changes in gene expression could lead to persistent structural changes in synapses, hence in the relevant neural networks.

Behavioural changes induced by acute pain can contribute to the transition to chronicity. Patients may respond to acute low back pain by prolonged and exaggerated inactivity or by adopting an abnormal posture or gait. Such secondary behavioural changes, if maintained over time, can actually trigger painful disorders of the spine. Emotional and cognitive responses of the patient and associates are the other dimensions of pain behaviour that can contribute to chronicity of pain. This is beyond the scope of this paper, however.

CONCLUSION
The type of pain that brings people to seek orthopaedic help should not be understood in terms of activation of nociceptive sensory endings alone. Currently there is an explosion of knowledge of neurobiology and the molecular nature of neuroplasticity. Changes do occur at different levels of transmission, including regulation of peripheral and central sensitisation. Increased knowledge of the neural mechanisms of pain benefits orthopaedic surgeons in the following ways: understanding of pain in clinical settings, awareness of new pain management modalities, and perhaps providing an opportunity to prevent transition to chronicity, similar to pre-emptive analgesia.

REFERENCES

The Authors
YU Kong-San, FHKCOS, FHKAM (Orth Surg), Department of Orthopaedics and Traumatology, North District Hospital, Fanling, Hong Kong.
CHAN Ping-Tak, FHKCOS, FHKAM (Orth Surg), Department of Orthopaedics and Traumatology, North District Hospital, Fanling, Hong Kong.