**Physiology and pathophysiology of chronic pain (Part I)**

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Chronic pain affects a significant proportion of the population. It negatively affects wellbeing, quality of life and productivity. To improve the effective management of chronic pain it is essential to understand pain physiology. The aim of this review is to discuss the physiology of pain as a foundation for understanding chronic pain. It describes the current definition of pain and classification of pain. Pain processing and pathways are also explained with emphasis on modulation of pain and its crucial role in pain perception. It also highlights the importance of multidisciplinary pain management.

**Keywords:** pain, chronic pain, physiology

**Introduction**

Chronic pain imposes a significant health burden on society and has a debilitating impact on individuals and their productivity.1 Chronic pain has been reported to affect 20% of people worldwide.2 With the current world population at 7.8 billion, it is estimated that approximately 1.5 billion people suffer from chronic pain. The socioeconomic burden of chronic pain in the USA is between US$560 and US$635 billion annually.3 The impact of chronic pain in Africa is also worrisome: Nigeria has a prevalence 5.5%,4 while approximately 1 in 5 South Africans (18.3%) has been reported to suffer from chronic pain.5

Chronic pain needs to be regarded as a disease entity in addition to being a symptom of a disease. It remains a condition that is not effectively managed despite years of pain research.1 Understanding the physiology of pain is crucial for the effective diagnosis and management of chronic pain.

**What is pain?**

In 2020, the International Association for the Study of Pain (IASP) adopted the new definition of pain as ‘an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage’.6 This definition emphasises that pain results from a complex interaction of sensory, emotional, physical, cognitive, social, psychological and spiritual components that can be influenced by age, sex, environmental conditions and experiences. This complexity of aetiology draws attention to the importance of multidisciplinary management when treating pain. The new, updated definition of pain is based on the perception of the sufferer rather than an external observer.

Acute pain is a protective mechanism that serves important adaptive purposes. It is a vital early warning system which indicates the presence of a potentially harmful stimulus.7 It activates withdrawal responses to prevent further harm, localises noxious stimuli and minimises mobility, thus promoting healing. However, pain becomes a burden when it outlives its adaptive usefulness.8 Any pain that persists beyond normal tissue healing time, which is presumed to be three months, is described as chronic pain. It may last or recur for more than three months and may arise without any injury.9

**Types of pain**

The classification of pain is varied and complex depending on the criteria. It may be classified based on intensity (mild, moderate or severe), quality (sharp, burning or dull), duration (acute or chronic), localisation (superficial or deep, specific or diffuse) or anatomical area affected (headache, backache, limb ache, neck pain, abdominal pain, etc.).7

Pain can also be classified based on the conduction velocity of the pain stimulus (fast pain or slow pain). Fast pain is also referred to as ‘first pain’ because it is first felt when one is in contact with a noxious stimulus. It has a rapid onset, is highly localised and is characterised as sharp with a short duration. Fast pain is transmitted by myelinated Aδ fibres which have a conduction velocity of 5–30 m/s. Slow pain is also referred to as ‘second pain’ and is transmitted by unmyelinated C nerve fibres, with a conduction velocity of 0.5–2 m/s. Its onset is slow and it is characterised as dull, diffuse, burning and long lasting.10

The mechanistic classification of pain currently recognised by the IASP is divided into nociceptive, neuropathic and nociplastic pain.11 According to the IASP, nociceptive pain is ‘pain that arises from actual or threatened damage to non-neural tissue and is due to the activation of nociceptors’.12 It describes ‘pain that occurs in normal functioning somatosensory nervous system unlike in neuropathic pain where there is the occurrence of abnormal functioning’. Nociceptive pain is a high threshold, protective and adaptive response that is activated when one is in contact with actual or imminent noxious stimuli due to exposure to injury, inflammation or mechanical noxious stimulus. It engages a withdrawal response to minimise tissue damage and is typically acute.

Neuropathic pain is defined as ‘pain caused by a lesion or disease of the somatosensory nervous system’.12 This may result from
injury that directly affects the nerves or as a result of metabolic disorders like diabetes mellitus or vitamin deficiencies.8,11 This pain is usually chronic and usually persists beyond an expected recovery period.

Nociplastic pain refers to ‘pain that arises from altered nociception despite no clear evidence of actual or threatened tissue damage causing the activation of peripheral nociceptors or evidence of disease or lesion of the somatosensory system causing pain’.12 Nociplastic pain involves pain due to altered processing without any physical evidence or the absence of any recognisable damage, such as fibromyalgia. Notably, this type of pain is not a psychosomatic disorder.

Pain processing and pathways (nociception anatomy)

To fully comprehend the mechanisms involved in chronic pain, understanding the basic physiology of pain processing is essential. Pain processing involves four major processes: transduction, conduction, modulation and perception (Figure 1).

Transduction

Transduction refers to the conversion of one form of energy into another. In pain context, it is the conversion of external noxious mechanical, thermal or chemical stimuli into electrical signals. When these electrical signals reach a threshold, an action potential is generated and conducted along the nerve fibres. Transduction occurs at the free nerve endings that respond only to pain and these are called nociceptors. Nociceptors are ‘high-threshold sensory receptors of the peripheral somatosensory nervous system that are capable of transducing and encoding noxious stimuli’.13 They are found in varying quantities or concentrations in the periphery in joints, skin, cornea and visceral organs.8 The fingertips, hands, periosteum and face have high quantities of nociceptors, while lower quantities are found over the torso.14 Nociceptors are either specific to one type of pain modality (they respond to either mechanical or thermal noxious stimuli) or polymodal (respond to mechanical, thermal and chemical noxious stimuli).15

Noxious stimuli activate ion channels present on nociceptor terminals of free nerve endings that act as molecular transducers to depolarise these neurons, thereby setting off nociceptive impulses along the pain pathways.16 By opening these ion channels, the influx of Na⁺ and Ca²⁺ are allowed, resulting in depolarisation and the generation of an action potential. There are many ion channels or membrane receptors, some of which include transient receptor potential (TRP), acid-sensing ion channels (ASIC) and purinergic receptors.

Conduction

Conduction is the relay of nociceptive electrical signals from the periphery to the spinal cord. The primary afferent neurons are pseudo-unipolar, with peripheral and central branches, and cell bodies in the dorsal root ganglia (DRG).17 The peripheral branch of a DRG neuron terminates in various tissues and organs, which receive different sensory modalities, while the central branch transmits impulse sensations to the spinal cord via the dorsal horns.18

The electrical signal generated in the nociceptors is conducted via the nerve fibre to the DRG and terminate in the dorsal horn of the spinal cord where they transmit to second-order neurons. The electrical signals stimulate the release of glutamate as a neurotransmitter from the presynaptic neuron, which binds to α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptors on the postsynaptic neuron in the substantia gelatinosa of Rolando. Substance P can also be released, especially when the pain is excessive.9

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**Figure 1:** Pain pathways (spinal and supraspinal)
The signal generated at the dorsal horn is then transmitted via the lateral spinothalamic tract (neospinthalamic or paleospinthalamic tract) which crosses to the opposite side of the spinal cord and ascends to the thalamus prior to transmission to the cerebral cortex. Multiple other pathways are also involved in the transmission of pain signals – these include the spinoreticular, spinomesencephalic, spinohypothalamic and spinoparabrachial tracts, but the spinothalamic tract is considered to be the main nociceptive pathway. The other pathways are mostly involved in the cognitive, motivational and affective aspects of pain processing, while the spinothalamic projections convey information on the intensity, localisation and discrimination of the noxious stimuli.

In addition, slow pain is transmitted to the reticular formation and all areas of the cerebral cortex (anterior cingulate cortex, insular cortex, primary somatosensory [S1], secondary somatosensory [S2] and prefrontal cortex). The signals carried to areas outside the cortical centres, especially the reticular formation, are for arousal rather than sensory discrimination of pain.

Transmission of pain in the face is slightly different from nociceptive transmission in other parts of the body. Nerve fibres carry nociceptive inputs from the ipsilateral portion of the face to the subnucleus caudalis in the spinal trigeminal nucleus, located in the lateral medulla of the brain stem. From there the signal travels to the contralateral thalamus via the anterior trigeminothalamic tract to the brain areas, similar to other parts of the body.

Modulation

Modulation is a process where pain signals are modified by suppressing or enhancing pain input signals.

Descending inhibition

This pathway produces a top-down modulation of afferent inputs at the dorsal horn. It originates primarily from the rostroventral medulla (RVM), periaqueductal grey matter (PAG), medullary reticular nuclei of the gigantocellular complex and the locus coeruleus. The raphespinal tract is the primary descending inhibiting tract that arises from the raphe magnus nucleus of the RVM. The RVM is the last and major relay for descending modulation of pain transmission in the spinal cord.

The PAG receives input from cortical areas (hypothalamus, amygdala, prefrontal cortex, anterior cingulate gyrus, nucleus accumbens) and the ascending fibres via the spinoparabrachial tract. The PAG exerts opioid-mediated inhibition of nociception in the dorsal horn of the spinal cord by activating the RVM. The RVM (which comprises the raphe magnus nucleus, gigantocellularis pars alpha and nucleus paragiganto cellularis lateralis), in addition to the PAG, also receives signals from the thalamus, the parabrachial nucleus and the locus coeruleus. The RVM sends serotonergic and noradrenergic projections to the dorsal horn of the spinal cord causing inhibition of nociceptive signals either directly or via activation of spinal interneurons. It is important to note that serotonin plays a role in both descending inhibition and facilitation, depending on the receptors involved. 5HT2 and 5HT3 are involved in descending facilitation while 5HT7 and 5HT2A are involved in descending inhibition. Generally, serotonin is thought to be predominantly facilitatory rather than inhibitory.

Descending facilitation

Facilitatory influence originates from supraspinal areas and relay at the RVM. The RVM has a bidirectional activity – it can also cause descending facilitation of nociceptive signals. Evidence exists that the RVM has an ‘ON’ and ‘OFF’ switch. Opioids exert analgesia by inhibiting the ‘ON’ cells and activating the ‘OFF’ cells. A disruption of the balance between the descending inhibition and facilitation activity contributes significantly to development and maintenance of chronic pain states.

Gate Theory of Pain

The Gate Theory of Pain was proposed by Ronald Melzack and Charles Patrick Wall in 1965 to explain certain pain processes. In summary, it suggested the process of how thick myelinated Aβ nerve fibres, that carry touch sensations, inhibit pain signals conveyed by C and Aδ nerve fibres. This theory explains why vigorous touch sensations, like rubbing or massage, alleviate pain. They proposed that sensations carried by the unmyelinated C, thin myelinated Aδ and thick myelinated Aβ nerve fibres all synapse in dorsal horn of the spinal cord at the substantia gelatiosa. This point of synapse is regarded as the gateway for pain. Melzack and Wall postulated that the thick myelinated Aβ nerve fibres indirectly close the gate by inhibiting the transmission of pain signals via the activation of interneurons in the substantia gelatiosa.

The thin unmyelinated C nerve fibres can also open the gate that increases synaptic transmission. The theory further suggested that the descending inhibitory pathways act on this gate to modulate pain transmission. Stress-induced analgesia, where pain is suppressed until after a stressful episode has passed, is also explained by this theory. An example of this is pain that occurs some hours after a fight. This is also the proposed mechanism for the analgesic activity of transcutaneous electrical nerve stimulation (TENS).

Descending facilitation/augmentation of pain signals can occur at the gate when the conditions favour opening of the gate. Generally, it is believed that modulation of pain is exerted via the gate control system to either augment or suppress it. This activity can be influenced by various factors such as mental state, exercise or stress.

Perception

Perception is the interpretation of the input signals by the cerebral cortex. This process involves multiple different brain regions. Signal interpretation depends on context, past experiences, expectations, and so on. In addition to the sensory aspect, pain perception has emotional, motivational and...
cognitive components that are processed in different areas of the cerebral cortex (limbic structures, anterior cingulate gyrus, prefrontal and insular cortices). These components usually account for the associated suffering experienced beyond the sensory perception and are expressed as a behavioural or psychological response. This concept reinforces the subjective nature of pain and the reason why pain is experienced differently among individuals.

Various emotional states can modulate how we perceive pain; thus non-pharmacological methods like distraction and behavioural therapy or placebo can be used to manage pain. The cortical areas involved in processing the subjective components of pain are referred to as the neuromatrix. The major components of the neuromatrix are the anterior cingulate cortex (ACC), the insular cortex (IC), the primary and the secondary somatosensory cortices (S1 and S2), the prefrontal cortices and the thalamus.

Conclusion
This review discussed the events involved in pain processing and the sites at which those events occur. It forms a premise for the understanding of pain, as well as the transition from acute to chronic pain, which will be covered in the second part of this review.

Conflict of interest
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Ethical approval
This submission is in accordance with the principles laid down by the Responsible Research Publication Position Statements as developed at the 2nd World Conference on Research Integrity in Singapore, 2010. This article does not contain any studies with human or animal subjects.

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