

Pain physiology and pain pathways

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The presence of pain is a protective mechanism that serves to prevent the body from further harm. However, when pain becomes pathological, it becomes a socio-economic disease burden that impacts a significant portion of the population.

This article aims to discuss the physiology of pain that forms the basis for understanding the processes that allow pain to become chronic. It describes the definition of pain and the various types of pain receptors involved in the processing and perception of pain. The physiology, pathways and processes involved in the activation and ongoing experience of pain are well described in terms of four distinct events, known as transduction, transmission, modulation, and perception.

The events described lend emphasis to the subjectivity of pain and the importance of a multidisciplinary approach to the effective management of chronic pain conditions.

Keywords: pain physiology, pain pathways

Introduction

The presence of pain serves as a physiologically protective mechanism by minimising movement, thus promoting healing and inducing a withdrawal reflex that protects from further harm.¹ Pain becomes pathological or chronic when it extends over a long period, usually defined as three months, or represents low levels of pathology that do not explain the presence or severity of pain.^{1,2} The result is a disease burden reported to affect one out of five South Africans and 20% of the population worldwide.¹ Therefore, a thorough understanding of pain physiology is crucial in the diagnosis and effective management of chronic pain conditions.

What is pain?

The phenomenon of pain was first described in 1979 by the International Association for the Study of Pain (IASP), updated in 2020, and is now defined as an unpleasant sensory and emotional experience associated with or resembling – as opposed to being described as such – actual or potential tissue damage.^{3,4} The new definition emphasises that the inability to verbally communicate or express pain does not invalidate the experience thereof.^{2,3} Pain is not specific to age, sex, or species, and is a subjective experience influenced by physical, psychological, social, spiritual, and environmental factors.¹ Consequently, a multidisciplinary approach to pain management is a critical and non-negotiable necessity.

Pain receptors

Nociceptors are present as free nerve endings of nerve fibres in skin, muscles, joints, and viscera.² There are three types of nociceptors:

- High-threshold mechanoreceptors respond to pinch and pinprick.⁴
- Silent nociceptors are activated when sensitised by inflammatory mediators.⁴
- Polymodal nociceptors respond to extreme temperatures, excessive pressure, and noxious chemical substances, such as hydrogen ions, potassium, adenosine triphosphate, bradykinin, serotonin, cytokines, and histamines.⁴⁻⁶ They are further sensitised to low-intensity stimuli by prostaglandins, leukotrienes, and the excitatory neurotransmitters calcitonin gene-related peptide (CGRP), substance P, and glutamate.⁴⁻⁶ Protons and serotonin act directly on ion channels on the cell membrane, but other sensitisers may bind to membrane receptors and activate second-messenger systems via G-proteins.⁴

Patterns of gene expression and the presence or absence of certain markers have been used to identify or define subtypes of nociceptors.⁴ Voltage-gated sodium channels (VGSC) Nav 1.7, tetrodotoxin-resistant Nav 1.8, and Nav 1.9 are expressed exclusively in the cell bodies of nociceptors. The Piezo-type mechanosensitive ion channel component (PIEZO2) and the transient receptor potential vanilloid receptor (TRPV1) are examples of such markers.^{4,7} TRPV1 and PIEZO2 are thermal and mechanically sensitive ion channels that have a role in allodynia, which is defined as pain due to a stimulus that does not normally provoke pain.⁴ TRPV1 is activated by capsaicin, hydrogen ions, and heat.^{2,4,6} PIEZO2, on the other hand, is the major mechanical sensor in nerves required for the perception of touch.^{4,7}

Pain processing and pathways

The processes involved in the activation and ongoing experience of pain are better understood when described in terms of four distinct events that allow the nociceptor to convey noxious information from peripheral tissues to the central nervous system.² These events are known as transduction, transmission or conduction, modulation, and perception.⁵

Transduction

Transduction is the process of converting the “energy” from a noxious stimulus into an electric signal or action potential, which is then transmitted along first-, second- and third-order neurons.^{1,2,5,6} The generator potentials responsible for the production of an action potential are the resting and threshold potentials of a neuron, which are approximately -70 and -55 mV, respectively.^{2,9} When threshold potential is achieved, the sodium voltage-gated channels present on first-order neurons open, which act as molecular transducers, resulting in the influx of sodium and the depolarisation of the neuron.^{1,2,8,9} Once the peak potential of +30–40 mV is achieved, potassium channels open allowing the efflux of potassium, leading to the repolarisation of the neuron.^{8,9}

First-order neurons have a single bifurcated axon, sending one end to peripheral tissues and the other end to the dorsal horn of the spinal cord grey matter where they synapse with second-order neurons.⁶ They are the site of energy transduction and have cell bodies that lie within the dorsal root or trigeminal ganglia and serve as the supply depot for the neuron, supplying the nerve with the proteins, lipids, and neurotransmitters needed for action potential propagation and pain transmission.² In the presence of nerve injury, an increase in the production of transducer proteins, sodium channels, and inflammatory receptors and proteins occurs within the cell body, making the nociceptive more responsive to stimuli.^{2,4,5}

Two main types of first-order neuronal sensory fibres respond to noxious stimuli. Firstly, slow-conducting unmyelinated C-fibres transmit dull and diffuse pain. Secondly, fast-conducting thinly myelinated A-delta fibres transmit sharp and well-localised pain.^{4,6-9} Thickly myelinated A-beta fibres were thought to respond mainly to non-painful stimuli, such as vibration and light touch.^{4,7} However, there is emerging evidence of their role in ultrafast nociception.^{4,7}

Transmission

When the action potential generated by the first-order neuron reaches the axon terminal, calcium enters the presynaptic terminal through calcium voltage-gated channels leading to the release of glutamate, which then crosses the synaptic cleft to activate the postsynaptic AMPA (alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) receptor.^{1,9} This leads to the transmission and propagation of the noxious signal to ascending tracts, such as the spinothalamic and spinoreticular tracts, which then relay the signal to third-order neurons.^{1,4,6} Whilst the action

potential threshold is regulated by potassium and calcium voltage channels, sodium voltage-gated channels Nav 1.7, Nav 1.8, and Nav 1.9 determine the threshold for initiation.^{2,9} The channel responsible for signal propagation, however, is Nav 1.6.^{2,9}

In the dorsal horn, first-order neurons synapse with second-order neurons, which in turn synapse in thalamic nuclei with third-order neurons.⁶ As the fibres of first-order neurons enter the spinal cord, they segregate according to size, with small unmyelinated fibres becoming medial, and larger myelinated fibres becoming lateral.⁶ Although most enter the dorsal horn in the ventrolateral bundle of the dorsal (sensory) root, 30% of C-fibres enter via the ventral (motor) root.^{4,6} For this reason some patients will continue to feel pain even after transection of the spinal root.⁶ A-beta fibres enter medial to the dorsal horn and pass without synapse to the dorsal columns.⁴ Upon entry, the nerve roots may ascend or descend one or two segments higher or lower than the segment of origin before synapsing with second-order neurons.⁶ Some communicate with second-order neurons through interneurons.⁶

The dorsal horn is divided into six Rexed laminae.^{4,6} A-delta fibres terminate in laminae I and V and are the important areas for the modulation and localisation of pain.⁴ Laminae I and V also represent the points of convergence between somatic and visceral afferent fibres, which are represented clinically by referred pain.⁶

A-beta and C-fibres that terminate in lamina II, also known as the substantia gelatinosa, send collateral branches to the dorsal horn which terminate in several laminae.^{4,6} A-beta fibres also synapse directly with terminals of C-fibres in lamina II.⁴

There are three types of second-order neurons:

- Nociceptive specific neurons are found in laminae II and III and respond to high-threshold noxious stimuli.^{4,6}
- Wide dynamic range (WDR) neurons are found in laminae V and VI and respond to a range of sensory stimuli.^{4,6}
- Low-threshold neurons respond to innocuous stimuli.⁴

Whilst the axons of some second-order neurons may ascend to higher centres ipsilaterally, most located in laminae I and V decussate close to their dermatomal level of origin to the contralateral side of the spinal cord before forming the spinothalamic tract. The tract lies anterolaterally in the white matter of the spinal cord and divides into the lateral and medial tracts.^{1,4,6}

The lateral (neospinothalamic) tract fibres contain axons of second order neurones located in laminae I and V which contribute to thermal and pain sensations.⁴ The fibres project to the ventral posterolateral nucleus and carry discriminative aspects of pain such as location, duration, and intensity.^{4,6} This is achieved through lateral thalamic third-order neurons that project to the primary and secondary somatosensory cortices in the postcentral gyrus and Sylvian fissure of the cerebral cortex respectively.^{1,4,6}

The axons of the medial (paleospinothalamic) tract fibres are located in lamina I and project to the medial thalamus.^{4,6} Projections from the spinoparabrachial tract are also responsible for mediating the autonomic and emotional aspects of pain via medial thalamic third-order neurons that project to the insula, hippocampus, amygdala, anterior cingulate gyrus, and prefrontal cortex.¹ Other ascending tracts include the spinoreticular tract, which is thought to mediate the arousal and autonomic responses to pain, the spinomesencephalic tract that projects neurons to the periaqueductal grey (PAG) where descending inhibitory pathways are located, the spinohypothalamic and spinohypothalamic tracts that activate the hypothalamus and evoke emotional behaviour, and the spinocervical tract that ascends uncrossed to the lateral cervical nucleus.^{1,6} Some fibres in the dorsal columns that carry light touch and proprioception can respond to pain.⁶ These fibres ascend medially and ipsilaterally.⁶

Modulation

The dorsal horn is where modulatory interactions between excitatory and inhibitory interneurons and descending inhibitory tracts from higher centres occur.^{4,6} Modulation of pain signals can occur peripherally or centrally and can facilitate or inhibit pain.^{1,6}

i. Peripheral modulation

Sensitisation of the nociceptor results in a decrease in the firing threshold, an increase in the frequency discharge to the same stimulus intensity, a decrease in response latency, and spontaneous firing even after the stimulus is no longer present.^{4,6} This results in primary hyperalgesia defined as an increased pain response to a painful stimulus.³

Secondary hyperalgesia is characterised by red flushing around the site of injury and local tissue oedema and occurs due to the release of substance P and CGRP.^{6,9} Substance P degranulates histamine from mast cells, and serotonin from platelets, and is also a potent vasodilator and chemoattractant for leukocytes.^{6,9}

ii. Central modulation

Three mechanisms are responsible for central sensitisation at the level of the spinal cord:

- Wind-up or temporal summation and sensitisation of second-order WDR neurons.^{6,9} With sustained transduction, substance P and neurokinins A and B are released from the presynaptic terminal.^{1,9} These produce a longer-lasting depolarisation of the postsynaptic membrane, resulting in the summation of postsynaptic depolarisations.^{6,9} Once the membrane is sufficiently depolarised, the physiological magnesium block of the postsynaptic NMDA (N-methyl-D-aspartate) receptor is removed.⁹ Glutamate then binds to the receptor, allowing the ion channel to open and produce a large calcium influx.⁹ Activation of the NMDA receptor results in the formation of nitric oxide, which facilitates the release of excitatory amino acids in the spinal cord.⁶
- Receptor field expansion is achieved by the recruitment of dorsal horn neurons of adjacent neurons that become

responsive to noxious and non-noxious stimuli to which they were previously unresponsive.⁶

- Enhancement of flexion reflexes observed both ipsilaterally and contralaterally.⁶

Pain suppression is dependent on supraspinal inhibition from higher centres, activity in A-beta collaterals and segmental (spinal) inhibition by endogenous opioids, cannabinoid systems, and inhibitory amino acids such as gamma-aminobutyric acid (GABA) and glycine.^{4,6}

In 1965, Melzack and Wall proposed that lamina II inhibitory interneurons can be activated directly or indirectly (via excitatory interneurons) by stimulation of non-noxious A-beta afferents from the skin, which would then suppress transmission in C-fibre afferents and therefore block the pain.^{1,4,6} This gateway theory is the working mechanism behind rubbing a painful area and the use of transcutaneous electrical nerve stimulation (TENS) in pain management.⁴

The descending tracts located in the PAG and nucleus raphe magnus (NRM) play a role in the descending inhibition of pain.^{1,4,6,9} The PAG receives inputs from the thalamus, hypothalamus, and cortex, as well as collaterals from the spinothalamic tract.^{4,6,9} PAG neurons excite cells in the NRM that in turn project to the dorsal horn neurons to block pain signals.^{4,6} The NRM is a descending system of serotonin-containing neurons, the stimulation of which results in the release of serotonin, providing profound analgesia.⁴ The cell bodies of these neurons are located in the raphe nuclei of the medulla and the axons synapse to cells in laminae II and III.⁴ Inhibitory adrenergic pathways originate primarily from the PAG and reticular formation and mediate their anti-nociceptive effect through activation of presynaptic and postsynaptic alpha-2 adrenergic receptors via noradrenaline.^{4,6}

The serotonergic and endogenous opiate system that acts via methionine, enkephalin, leucine enkephalin, and β -endorphin is primarily mediated by the NRM and reticular formation.⁶ These opioids act presynaptically to hyperpolarise first-order neurons and inhibit the release of substance P.⁶ Exogenous opioids act primarily on postsynaptic second-order neurons or interneurons in lamina II.⁶

Perception

The thalamus is the key area for processing information from third-order neurons that project to the cerebral cortex.^{1,4,6} The cortical areas involved in this process are referred to as the neuromatrix and comprise the anterior cingulate cortex, insular cortex, primary and secondary somatosensory cortices, and the prefrontal cortex.¹

The combined process input from third-order neurons evokes pain cognition, perception, and the behavioural response to pain.^{1,4,6} Noxious signal interpretation is thus subjective and dependent on expectations and past experiences, as well as biological and environmental factors.¹ These factors collectively lead to behavioural and psychological responses best addressed

by a multidisciplinary team when managing chronic pain conditions.¹

Conclusion

The events involved in pain conduction from the peripheral nervous system to the central nervous system form the foundational aspects of pain physiology and help to further understand the complex processes that result in chronic pain.

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