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Review Article

Pathways of Pain

Pathways of Pain: An Anatomical Perspective on Transmission and Modulation

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Pain is a complex sensory-emotional experience essential for survival, serving as an imperative warning system for the body. The article provides an anatomical overview of pain transmission and modulation, describing the pathways and structures involved in nociception. Pain transmission begins by activation of nociceptors in peripheral tissues, converting noxious stimuli to electrical signals conveyed via A-delta and C fibers to the dorsal horn of the spinal cord. Second-order neurons convey the information along ascending pathways, primarily the spinothalamic tract, to supraspinal brain centres like the thalamus, somatosensory cortex, limbic system, and prefrontal cortex, where pain is perceived and interpreted. Pain modulation occurs at different levels of the nervous system and is mediated through inhibitory as well as facilitatory mechanisms. Descending control from the brainstem -periaqueductal gray (PAG), and rostral ventromedial medulla (RVM) - plays a crucial role in modulating transmission of nociception at the spinal level. The neurotransmitters serotonin, norepinephrine, GABA, and endogenous opioids are the main modulators of pain. An understanding of pain transmission and modulatory mechanisms at the physiological and anatomical levels is essential for the planning of targeted pain management and treatment approaches.

Keywords: Pain, Modulation, Nociception, Periaqueductal gray, rostral ventromedial medulla, GABA

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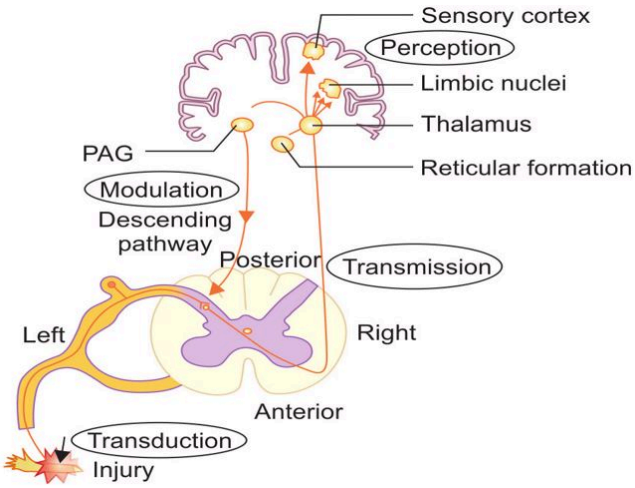
Introduction

The perception of pain is a complex phenomenon that is influenced by emotional state and past experiences of the individuals, pain is the sensation that warns of potential injury and alert the person to avoid or treat it.[1] Pain is an essential physiological response that observes to alert the body to potential or actual tissue damage, facilitating protective behaviour, however, its mechanism is far from simple involving complex pathway within the periphery and central nervous system. Understanding the pain pathways is crucial not only for normal pain mechanisms but also for addressing chronic pain conditions that results from dysfunction in the system.

Basic Mechanism of Pain Pathway (Nociception)



Tabular overview of Pain pathway

Stage	Location	Function	Key Components
1. Transduction	Peripheral tissues (skin, muscles, viscera)	Conversion of noxious stimuli (chemical, mechanical, thermal) into electrical impulses	Nociceptors (free nerve endings of Aδ and C fibers)
2. Transmission	Peripheral nerves → spinal cord → brain	Propagation of pain signals to the CNS	Aδ fibers (sharp pain), C fibers (dull pain), dorsal horn, spinothalamic tract
3. Perception	Thalamus and cerebral cortex	Awareness and interpretation of pain	Thalamus, somatosensory cortex, limbic system
5. Modulation	Brain→ descending pathway	enhance or suppress the pain.	Brain, periaqueductal gray, raphe nuclei

All these leads to one end result, and the pathway of pain has been initiated and completed, thus Allowing Us to Feel the Painful Sensation Triggered by The Stimulus.

Pain Pathway from Periphery to Central

1. Peripheral Nervous System (PNS)

The pain pathway starts in the peripheral nervous system, and there are specialized sensory neurons known as nociceptors that are responsible for detecting dangerous stimuli. The nociceptors are found throughout the body on the skin, muscle, joints, and internal organs.

Nociceptors

Nociceptors are specialized sensory receptors responsible for detecting noxious (harmful or potentially damaging) stimuli, which can result in the sensation of pain. They are a key component in the peripheral nervous system and initiate the pain pathway through transduction.

Types of Nociceptors

Nociceptors are classified based on the type of stimulus they respond to:

1. Mechanical Nociceptors - Respond to pressure, pinch, or mechanical deformation (e.g., cutting or crushing).

2. Thermal Nociceptors - Activated by extreme temperatures (hot or cold).

3. Chemical Nociceptors - Respond to chemical irritants (e.g., acids, capsaicin, inflammatory mediators like bradykinin).

4. Polymodal Nociceptors - Respond to multiple types of noxious stimuli (mechanical, thermal, and chemical).

These are the most common type found in skin, joints, muscles, viscera (internal organs), and cornea. The cell bodies of nociceptors reside in the dorsal root ganglia (for the body) and trigeminal ganglia (for the face).

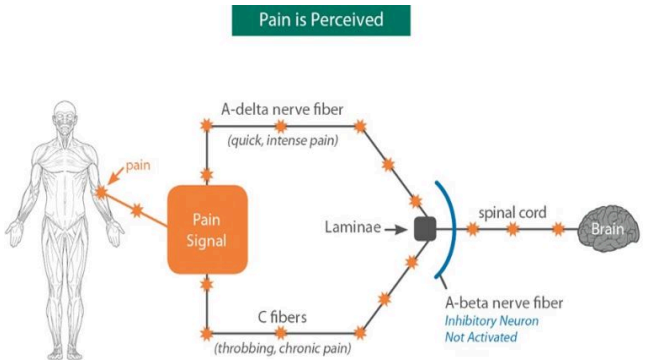
Activation of Nociceptors

Nociceptors are activated when tissue damage or intense stimuli cause Influx of Na^{+} and Ca^{2+} generating an action potential Transmission of the signal along the axon to the spinal cord.

Nerve Fibers and Transmission

The primary nerve fibers involved in pain transmission are A-delta fibers and C fibers.[2]

A-delta Fibers are lightly myelinated, have a medium diameter, and conduct impulses at 5–30 m/s, mediating sharp, well-localized pain. **C Fibers** are unmyelinated, small in diameter, and conduct slowly at 0.5–2 m/s, typically carrying dull, burning, or aching pain. These fibres arise from nociceptors and are responsible for the (fast) and (slow) pain responses.[3]



	A β fiber	A α fiber	C fiber
Diameter	Large	Small	Smallest
Myelinated	Highly	Thinly	unmylineted
Conduction velocity	>40ms-1	5-15ms-1	<2ms-1
Receptor activation threshold	Low	High and low	High
Sensation of stimulation	Low touch, non-noxious	Rapid, sharp, localised pain	Slow diffuse, dull pain

Nociceptors send signals via two main types of nerve fibers. These fibers enter the dorsal horn of the spinal cord through the dorsal roots, where they synapse with second-order neurons.

Signal Transduction

Pain signal transduction starts when nociceptors detect harmful stimuli and convert them into electrical signals.[4] Activation of ion channels (like Na^+ channels) leads to depolarization and action potential generation in afferent fibers.[5] These signals are transmitted to the central nervous system, where neurotransmitters like glutamate and substance P are released. Glutamate activates excitatory receptors, while substance P binds to NK-1(neurokinin 1) receptors, amplifying and propagating the pain signal.[6]

2. Spinal Cord

Once pain signals reach spinal cord, they synapse with second-order neurons in dorsal horn.

This region of the spinal cord plays a critical role in processing and modulating pain signals. The pain information is then transmitted to the brain via ascending pathways, primarily the spinothalamic tract.

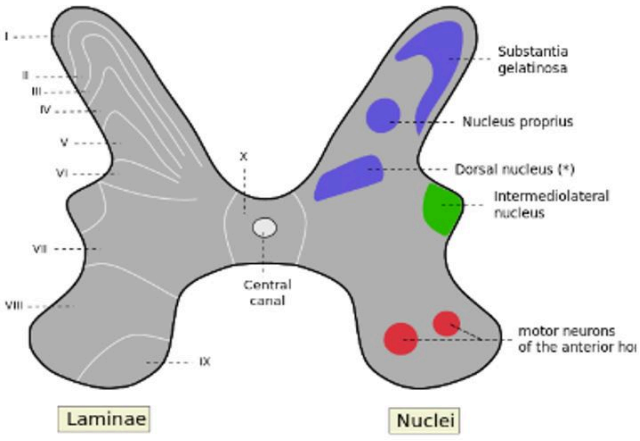
Dorsal Horn Processing

The dorsal horn of the spinal cord plays a critical role in receiving and modulating sensory inputs, particularly nociceptive, thermal, and mechano-receptive information. It is organized into distinct layers known as Rexed laminae, which correspond to specific functions and afferent inputs.

Lamina Layers

The laminar organization of the dorsal horn was first described by Bror Rexed, dividing the gray matter into ten laminae based on cytoarchitecture.[7] Laminae I–VI are located in the dorsal horn and are functionally distinct:

- **Lamina I (Marginal Zone):** Receives noxious and thermal input via Aδ and C fibers; projects to the **spinothalamic tract**[8]
- **Lamina II (Substantia Gelatinosa):** Modulates nociceptive input from C fibers; rich in interneurons and targets of **opioids** and **inhibitory neurotransmitters**.
- **Laminae III–IV (Nucleus Proprius):** Process **non-painful touch** (Aβ fibers); contribute to reflexes and ascending sensory pathways.[9]
- **Lamina V:** Contains **wide dynamic range (WDR) neurons** integrating Aβ, Aδ, and C fiber input; involved in **referred pain** and **polymodal processing**.
- **Lamina VI:** Processes **proprioceptive** input, mainly from muscles, especially in limb-related spinal segments.



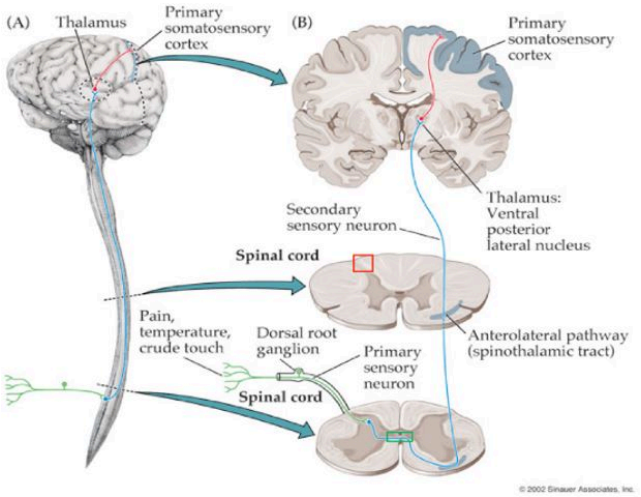
Neurotransmitters

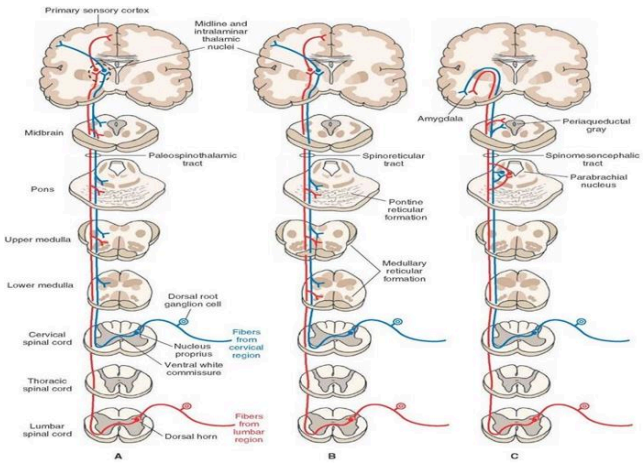
Processing of the senses within the dorsal horn is controlled by a balance between excitatory and inhibitory neurotransmitters:

- Excitatory Neurotransmitters: Glutamate is the main excitatory neurotransmitter released by all primary afferent fibers stimulating second-order neurons in the dorsal horn to convey pain information. Substance P, which is primarily released by C fibers, binds to neurokinin-1 (NK-1) receptors and significantly mediates slow, chronic pain. Frequently co-released with substance P, calcitonin gene-related peptide (CGRP) facilitates pain transmission and induces vasodilation, as part of the total pain response.
- Inhibitory Neurotransmitters: GABA (Gamma-Aminobutyric Acid): Receptors to suppress pain transmission on pre- and postsynaptic levels and Endogenous Opioids (Enkephalins, Endorphins): Interact with opioid receptors on primary afferent terminals and interneurons, inhibiting release of excitatory neurotransmitters and blocking pain signals.**[10]**

Ascending Tracts

Features	Spinothalamic Tract[11]	Spinoreticular Tract	Spinotectal Tract
Origin	Dorsal horn (laminae I, II, V)	Dorsal horn (laminae V–VIII)	Dorsal horn (mostly laminae I and V)
Fiber Type	Mainly Aδ and C fibers	Mainly C fibers	Aδ and C fibers
Pain Type	Sharp, well-localized pain; temperature; crude touch	Dull, aching, poorly localized pain	Noxious and sensory stimuli integration
Course	Contralateral in anterolateral funiculus	Bilateral in anterolateral funiculus[12] (some fibers decussate)	Contralateral in anterolateral funiculus
Primary Relay	VPL nucleus of the thalamus	Reticular formation (medulla, pons, midbrain)	Tectal area (especially superior colliculus)
Final Projection	Primary somatosensory cortex	Intralaminar thalamic nuclei → cortex, hypothalamus, limbic system	Midbrain tectum (visual/auditory reflex centres)
Main Function	Sensory discrimination and localization of pain	Emotional, arousal, and autonomic responses to pain	Reflexive head/eye movement toward stimuli





3. Brain

The brain processes pain signals through several regions, including:

Thalamus: Serves as primary relay station for pain messages, sending nociceptive information to various cortical regions. m/sedial dorsal nucleus communicates with prefrontal cortex & limbic system, affecting affective & cognitive properties of pain.

- **Primary Somatosensory Cortex (S1):** Found in the postcentral gyrus, S1 accurately identifies pain location and measures its magnitude, assisting in determining where and how much the pain is.
- **Limbic System:** Comprises the amygdala, hippocampus, and thalamic parts; involved in the emotional and behavioral reaction to pain, integrating its unpleasantness and distress.
- **Prefrontal Cortex:** Plays part in cognitively assessing pain, managing emotional reactions & decision-making regar. managing pain. It also has role in placebo reactions & pain modulation.

4. Descending Pain Pathways and Pain Modulation

Pain is modulated by the brain through descending pathways that are primarily from the periaqueductal gray (PAG) and the rostral ventromedial medulla (RVM). These descending pathways affect spinal cord processing of pain information by releasing neurotransmitters like serotonin, norepinephrine, and endogenous opioids that have either suppressive or facilitatory effects on pain transmission. Pain modulation refers to the physiological mechanisms for either enhancing or inhibiting pain perception. It combines both facilitatory ascending and inhibitory descending pathways so that the nervous system can adjust pain responses according to physiological state or psychological context. An important component is the descending pain inhibition system, which controls pain intensity by inhibiting nociceptive signals at the spinal cord level. This system can be stimulated by mechanisms like endogenous opioid release, stress, and expectations, and it has an important role in pain control and adaptation.

A) Periaqueductal Gray (PAG): The periaqueductal gray of the midbrain is a central site in the system of descending pain modulation. It engages pain reduction by sending messages to the rostral ventromedial medulla (RVM) and spinal cord in order to block nociceptive transmission. The PAG converges inputs from higher brain areas, such as the prefrontal cortex, hypothalamus, and amygdala, to facilitate pain modulation based on emotional and cognitive considerations.**[14]**

B) Rostral Ventromedial Medulla (RVM) The RVM participates in the terminal relay of descending pain modulation signals from the PAG to the spinal cord.

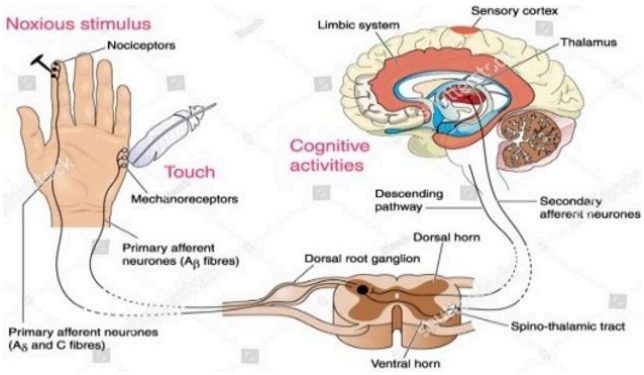
- It contains two types of cells:
- ON cells, which facilitate pain (by enhancing nociceptive signals).
- OFF cells, which inhibit pain (by suppressing nociceptive signals).

Pain Modulation

Gate Control Theory

The gate control theory is of pain was proposed by melzack and wall in 1965. The theory explains mechanism within the spinal cord in dorsal horn.

It was suggested that at the site where pain fibres enter the central nervous system, inhibition occurs by connector neuron excited by large, myelinated afferent fibre's carrying information of non-painful touch and pressure. The excess tactile stimulation produces by massage and application of liniment "closed the gate" for pain. Once the non-painful tactile stimulation ceased "gate was opened" and information on the stimuli ascended the lateral spinothalamic tract.**[15,16]**



Theory	Key Concept	Mechanism	Involved Structures
1. Gate Control Theory	Spinal"gate" modulates pain	Large Aβ fibers inhibit small pain fibers via interneurons	Dorsal horn (substantia gelatinosa, Lamina II)
2. Descending Pain Modulation	Brain inhibits spinal pain transmission	Descending pathways release inhibitory neurotransmitters	PAG, RVM, dorsolateral pontine tegmentum
3. Endogenous Opioid System	Body produces natural painkillers	Opioids bind to CNS receptors to suppress nociceptive signals	PAG, spinal cord, limbic system
4. Diffuse Noxious Inhibitory Controls (DNIC)	Pain inhibits pain	Distant noxious stimuli activate inhibitory pathways	Brainstem circuits, dorsal horn
5. Central Sensitization	Chronic pain leads to CNS hyperexcitability	Long-term potentiation, NMDA receptor activation	Dorsal horn neurons, thalamus, cortex

Discussion

Pain perception has a convoluted neural pathway that starts with nociceptors, which are specialized sensory neurons found in the skin, muscles, joints, and internal organs. Nociceptors recognize noxious stimuli, including excessive temperatures, mechanical pressure, or chemical irritants, and transmit them as electrical signals.

These fibers carry the signals through two main types of fibers: Aδ fibers, which are myelinated and carry sharp, well-localized pain quickly, and C fibers, which are unmyelinated and carry dull, aching pain more slowly. Once they get to the dorsal horn of the spinal cord, these primary afferent neurons synapse with second-order neurons. The axons of these second-order neurons decussate to the opposite side of the spinal cord and travel upward through several tracts, such as the spinothalamic, Spino reticular, and Spino mesencephalic tracts. The spinothalamic tract, especially its lateral portion, is mainly involved in carrying pain and temperature sensations to the thalamus, which forwards the information to the somatosensory cortex for accurate localization and perception of pain. Aside from these ascending routes, there are descending modulatory systems of the body that either enhance or suppress pain messages. Major structures participating in this modulation are the periaqueductal gray matter, raphe nuclei, and the locus coeruleus. These regions secrete neurotransmitters like serotonin and norepinephrine, which suppress pain transmission at the spinal level. Endogenous opioids such as endorphins and enkephalins are also important in inhibiting pain signals, helping to create the body's natural pain suppressant mechanism. These pathways are vital in developing good pain management because treatments can target various levels of the pain pathway to eliminate pain.

Conclusion

Transmission of pain in the human nervous system is a dynamic and highly integrated process comprising specialized peripheral nociceptors, intricate spinal cord networks, and several ascending and descending pathways that project to and from various brain regions. It has both somatosensory elements for pain localization and discrimination, as well as limbic-cortical loops for emotional and cognitive processing. Pain transmission is functionally regulated by excitatory and inhibitory inputs such as neurotransmitters, neuromodulators, and glial cell functions. Knowledge of these mechanisms is critical to the design of effective pain management and the enhancement of the quality of life in pain patients. Additional research into pain pathways and modulation can yield new treatments and therapies for pain relief.

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