

Chapter 16

THE PHYSIOLOGY OF ACUTE PAIN

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INTRODUCTION

The understanding of acute pain physiology has expanded greatly over recent decades, revealing increasing layers of complexity. This chapter aims to simplify and distil current thinking and tackle the central question of, “how do we feel pain?” Any such discussion

will necessarily touch upon numerous receptor types and pain pathways, but the chapter will focus on the principles of pain transmission and modulation, charting the journey from peripheral detection to the brain’s central experience of pain.

BASIC CONCEPTS

Pain is in itself a complex construct, defined by the International Association for the Study of Pain as an “unpleasant sensory and emotional experience associated with actual or potential tissue damage.” According to this definition, an intact nervous system is needed to transmit the signal and an intact consciousness must process it, with physiological and psychological factors able to influence the experience.¹ A concept of a body–self neuromatrix has been proposed in which multiple physiological and psychological inputs are processed to produce the output called pain.²

The ability to detect noxious stimuli that are actually or potentially associated with tissue damage is an essential protective defense mechanism; the neural

processing of such stimuli is called “nociception” and represents the sensory component of pain. Acute pain can therefore be thought of as beginning with transduction by peripheral nociceptors of a noxious stimulus via an electrical impulse, transmitted to the dorsal horn of the spinal cord, where signals are processed and potentially modulated by descending pathways from the periaqueductal grey (PAG). Signals then ascend via the thalamus to a higher “pain matrix” consisting of the primary and secondary sensory cortex, the insular cortex, the anterior cingulate cortex, and motor regions, including the cerebellum.¹ The limbic system feeds into this matrix, accounting for the modulatory effects of emotional state on pain perception (Figure 16-1).

PAIN MECHANISMS

Peripheral Nociceptors

Peripheral nociceptors are essentially afferent unmyelinated C-fibers and lightly myelinated A- δ fibers lying in the periphery that connect to the laminae of the dorsal horn of the spinal cord. The most numerous subclass of nociceptor is the C-fiber polymodal nociceptor, which responds to a broad range of physical and chemical stimuli.³ The sensory component of pain begins with the formation of an action potential in these afferent nerves and its transmission to the dorsal horn. C-fiber pain is classically described as burning or aching, whereas A- δ fibers, with their increased conduction velocities owing to myelination, transmit sharp or pricking pain and are involved in the protective reflex arc.

Nociceptor Receptors and Ligands

The process of an action potential being generated is complex, with numerous receptors and chemical ligands implicated; however, the underlying principle is simple: all the receptors serve one of two purposes, either to generate the threshold potential required by directly allowing ion movement, or to metabolically facilitate signal transmission, for example by effects on voltage-gated sodium channels.

Transient receptor potential vinnoid (TRPV) channels detect a range of thermal stimuli⁴ and can initiate signals purely in response to such stimuli (Table 16-1); however, the majority of receptors are activated by the chemical cascade associated with tissue damage. Injury to the tissue leads to disruption of the cells, allowing their contents to spill into the interstitium. This lowers pH, stimulates the inflammatory response with mast cell activation and degranulation, and induces enzymes such as cyclooxygenase-2. The net result is a cocktail of mediators including prostaglandins, hydrogen ions, bradykinins (BKs), serotonin (5-HT), potassium, adenosine triphosphate (ATP), histamine, nerve growth factor (NGF), and glutamate. These mediators act at a host of receptors to sensitize the peripheral nociceptors, including acid-sensing ion channels, BK-1 and BK-2 receptors, 5-HT_{2A} receptors, P₂X₃ (which binds ATP), and tyrosine kinase A (TrkA) receptors (which bind NGF).

Additional Peripheral Mechanisms

Additional mechanisms serve to perpetuate this painful response to tissue injury: neuropeptides such as substance P are released by the peripheral nerve terminals and contribute to the recruitment of serum factors and inflammatory cells at the site

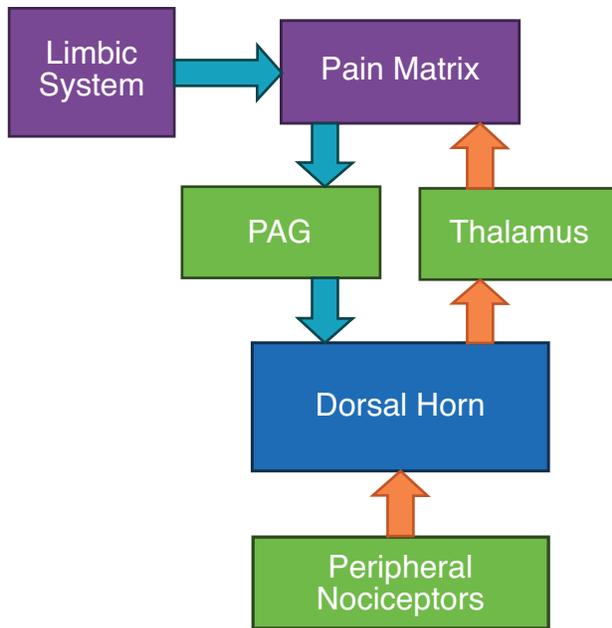


Figure 16-1. Simplified schematic of pain transmission. Orange arrows represent ascending pain pathways and blue arrows modulatory pathways. PAG: periaqueductal grey

of injury (neurogenic edema).³ Many inflammatory cells also express TrkA receptors, meaning that the presence of NGF can stimulate these cells to release further 5-HT and histamine. In addition, sympathetic nerve terminals release prostaglandins in response to BK.¹

The Dorsal Horn

The dorsal horn is essentially an integration center where primary inputs from the periphery can be significantly modified before being transmitted to the cortex. The cell bodies of the nociceptive afferents that innervate the trunk, limbs, and viscera are located in the dorsal root ganglia and project to the dorsal horn, while those innervating the head and neck are in the trigeminal ganglia and project to the trigeminal nucleus. The C-fiber and A- δ nociceptive afferents predominantly terminate superficially in laminae I and II of the dorsal horn, with some deeper A- δ projections to wide dynamic range neurons in lamina V, which encode both noxious and innocuous stimuli. A- β fibers transmit light touch or innocuous mechanical stimuli to laminae III and IV and are implicated in gate-control theory, which suggests that impulses in these fibers can reduce onward nociceptive traffic to the brain.⁵

Pain Transmission, “Wind-Up,” and Long Term Potentiation

Pain transmission in the dorsal horn between the primary and secondary afferents is predominantly mediated by the excitatory amino acid glutamate and the peptide substance P. Depolarization of the primary afferent terminal results in glutamate release into the synaptic cleft, which binds to postsynaptic ionotropic alpha-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate (AMPA) receptors. The AMPA receptors signal information related to the location and intensity of noxious stimuli.³ Usually a constant and predictable stimulus-response ratio is maintained during transmission.⁶

However, repeated C-fiber stimulation at the dorsal horn results in a progressively more depolarized postsynaptic membrane and in turn displacement of magnesium ions from N-methyl-D-aspartate (NMDA) receptors. The now vacant NMDA receptors can bind glutamate, which, in combination with glutamate’s action at metabotropic receptors and substance P acting at neurokinin-1 (NK₁) receptors, leads to the “wind-up” phenomenon. Essentially, a progressive increase or wind-up in output from the dorsal horn occurs in response to each stimulus. This change is evoked by low frequency C-fiber stimulation and manifests as an enhanced postsynaptic response during a train of stimuli.³

Associated with higher frequency stimulation, long-term potentiation (LTP) is similar to the wind-up phenomenon in the sense that output from the dorsal horn is increased, but, crucially, the enhanced response outlasts the conditioning stimulus; LTP has been implicated in learning and memory in the hip-

TABLE 16-1
TRANSIENT RECEPTOR POTENTIAL VALLINOID CHANNEL SUBTYPES

Subtype	Stimulus / Ligand
TRPV ₁	Heat (>42°C), hydrogen ions, capsaicin
TRPV ₂	Heat (>53°C)
TRPV ₃	Warm (>32°C)
TRPV ₄	Warm (>32°C)

TRPV: transient receptor potential vallinoid
Data source: Applied Physiology of Pain. In: Macintyre P, Scott D, Schug S, Visser E, Walker S, eds. *Acute Pain Management: Scientific Evidence*. 3rd ed. Australian and New Zealand College of Anaesthetists and Faculty of Pain Medicine; 2010:1-6.

pocampus and pain sensitization in the spinal cord.⁷ LTP is mediated by calcium influx through NMDA receptors activating intracellular kinases; these in turn bring about alterations in ion channel and receptor numbers on the postsynaptic membrane, leading to more efficacious neural transmission.³

Through similar cellular processes, repeated stimulation in the dorsal horn also leads to increased sensitivity in secondary afferents in close proximity to the directly stimulated area. This can result in intact tissue anatomically adjacent to the damaged area demonstrating hyperalgesia (increased response following noxious inputs).¹ This secondary hyperalgesia, together with wind-up and LTP, may contribute to central sensitization, which encompasses increased sensitivity to both C and A- β fiber inputs, resulting in hyperalgesia and allodynia (pain in response to previously nonpainful stimuli).⁷

Descending Modulatory Pathways

Signals originating in the cortex, hypothalamus, and amygdala are integrated in PAG in the brainstem, giving rise to a descending pathway that interacts at the synapse of the primary and secondary afferents in the dorsal horn. The pathway is rich in opioid receptors, allowing for modulation by both endogenous and exogenous opioids; 5-HT and adrenaline also function as neurotransmitters in this system.¹ The adrenergic component in particular is inhibitory at the dorsal horn and is likely, at least in part, to account for why combat casualties with very severe injuries, whose systems are flooded with adrenaline, experience little or no acute pain. Serotonergic pathways can be involved in pain inhibition, but they have also been implicated in facilitating pain transmission at the dorsal horn.⁸

Other local inhibitory systems at the dorsal horn that may provide future avenues for pharmacological intervention include the α -4- β -2 nicotinic acetylcholine receptor and cannabinoid receptor type 1.

Role of the Glia

Until recently, the glial cells had been thought to provide a framework to support the neurons performing "housekeeping" and homeostatic functions only¹; however, current research suggests that glial cell activation also plays a part in nociception due to release of neuroexcitatory products.⁹ The role of the glia is arguably more pronounced in the development of chronic pain, but these cells can also affect the transmission of acute pain.

Following peripheral tissue or nerve injury, microglia and astrocytes can shift to an activated state charac-

terized by the release of a plethora of proinflammatory substances including cytokines, chemokines, arachidonic acid, prostaglandins, excitatory amino acids, ATP, and NGF. These glial products have a modulatory effect on acute pain transmission, directly enhancing neuronal excitability and increasing pain-associated neurotransmitter release from sensory afferents. Key to this process is the up-regulation of the number and conductance of excitatory receptors such as AMPA and NMDA, and down-regulation of inhibitory receptors such as γ -aminobutyric acid (GABA) and glial glutamate transporters.⁹

The mechanism of glial activation is a complex process involving many putative transmitters released by neurons in response to injury. One receptor that may be key to the activation process is toll-like receptor 4 (TLR4)⁹; this receptor could represent a target for pharmacological intervention to mitigate the impact of glial cells on both acute pain transmission and the subsequent development of neuropathic pain.

Pain Perception in Higher Centers: The "Pain Matrix"

The spinothalamic tract carries signals from the primary afferent terminals in laminae I and II, via connections in lamina V of the dorsal horn, to the thalamus and then to the somatosensory cortex, conveying information on the site and type of painful stimulus. The spinoreticular and spinomesencephalic tracts ascend to the medulla and brainstem, allowing integration of nociceptive information with arousal and homeostatic and autonomic responses.³

The concept of a higher "pain matrix" aims to explain how different areas of the brain combine to produce the complex experience of pain. The somatosensory cortex is key to the matrix, responsible for the sensory component of pain and allowing comprehension of its location and nature. The insular cortex is thought to have a somatic representation of pain similar to the sensory cortex and seems to provide the affective component of pain; together with the cingulate and prefrontal cortex, it conveys the unpleasantness of pain.¹ Feeding into this matrix is the limbic system, which allows a person's emotional state to impact on pain perception.

It is now clear that the psychological context of the stimulus in terms of anticipation and attention can be as important as the stimulus parameters.⁸ Reported pain is less during tasks that require concentration, demonstrating how higher cortical function can modulate pain experience in a top-down fashion. The effect of anticipation, once dismissed as mediating anxiety-linked augmentation of pain only, now ap-

pears important in its own right by causing activation of most of the nociceptive system, although evoking

smaller responses than the responses related to pain intensity.¹⁰

CONCLUSION

Understanding of the physiology behind the experience of acute pain will unquestionably continue to develop in the future. Despite potentially clouding the understanding of basic transmission processes, the complexity already delineated has indicated exciting new possibilities for pharmacological research. The large number of receptor types involved throughout the nociceptive system clearly shows that no one drug will provide all the answers, and a truly multimodal approach to the management of pain must exploit more of these mechanisms, particularly in the periphery and at the dorsal horn.

Acute and chronic pain have traditionally been considered distinct clinical entities, but current thinking views them as a continuum of the same basic process, involving the same nociceptive tree.⁸ An understanding of the physiology of acute pain underpins research into how this system begins to function aberrantly in chronic pain. More importantly, the role of acute pain management in manipulating this physiology and preventing the transition to persistent pain must be further investigated. Pain and its treatment are discussed further in the following chapters in section 3 of this volume.

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