

Dual Inhibition and Optogenetic Regulation Targeting COX/5-LOX and TRPV1-Mediated Sensitization in the Neospinothalamic Pathway

 Tayfun Baser¹,  Mustafa Saygin²

1 Suleyman Demirel University, Institute of Health Sciences, Department of Physiology, Isparta, Türkiye

2 Suleyman Demirel University, Faculty of Medicine, Department of Physiology, Isparta, Türkiye

*Correspondence: Tayfun Baser; fizyolojityayfun@gmail.com

Cite as: Baser T, Saygin M. Dual Inhibition and Optogenetic Regulation Targeting COX/5-LOX and TRPV1-Mediated Sensitization in the Neospinothalamic Pathway. J Cukurova Anesth Surg. 2026;9(3):632-652. doi:10.36516/jocass.1840651

Received: 14.12.2025, Accepted: 14.09.2026, Published: 30.09.2026, CC-BY-NC-4.0

Abstract

The aim of this study is to elucidate the molecular sensitization mechanisms in the neospinothalamic pathway and to highlight that the limitations of current single-target therapies can be overcome with the novel experimental method of optogenetics. This study examines the neurophysiological dynamics, molecular basis, and novel therapeutic strategies involving optogenetics for pain perception within the neospinothalamic pathway, which is responsible for fast and localized pain transmission. During transduction, the initial phase of the pain signal, nociceptors (A-delta and C fibers) become sensitized by arachidonic acid metabolites released following inflammation. A key role in this sensitization is played by prostaglandins and leukotrienes, which are produced by the cyclooxygenase and 5-lipoxygenase enzymes. These molecules modulate the transient receptor potential vanilloid-1 ion channels, which respond to thermal and chemical stimuli, thereby increasing nociceptor excitability and leading to depolarization. The resulting electrical signal passes through a modulation phase in the dorsal horn of the spinal cord, culminating in perception in the thalamus and somatosensory cortex. It is suggested that future therapeutic strategies should focus on dual inhibitors that simultaneously target the cyclooxygenase and 5-lipoxygenase enzymes, alongside transient receptor potential vanilloid-1 antagonists, to provide more comprehensive analgesia.

Keywords: Neospinothalamic Pathway, Nociception, COX, 5-LOX, TRPV1, Optogenetic

1. Introduction

Pain is an experience that results from the pathological transformation of neurophysiological processes, significantly diminishing the quality of life.¹ Sensitization along the neospinothalamic tract, the primary axis for pain signal transmission, plays a pivotal role in pain pathogenesis.²

The molecular basis of this sensitization is formed by mediators produced following inflammation via the enzymes Cyclooxygenase (COX) and 5-lipoxygenase (5-LOX).³ These mediators hyperactivate the transient receptor potential vanilloid-1 (TRPV1) ion channels on nociceptors, thereby lowering the pain threshold.⁴

Current single-target pharmacological approaches are often inadequate and associated with side effects when faced with this multifaceted pathophysiology. This necessitates the development of synergistic and innovative strategies that can simultaneously target multiple critical pathways.⁵ Furthermore, optogenetic applications may hold a crucial role in managing pain processes.⁶

The purpose of this study is to elucidate the significance of dual inhibition in COX/5-LOX-mediated pain within the neospinothalamic pathway and to develop target-specific analgesia strategies by utilizing the advanced technique of optogenetic regulation.

2. Material and Method

The literature search for this review was conducted using the PubMed, Scopus, and Web of Science databases, covering publications from inception to the present day. The keywords used, in both Turkish and English, included: "pain," "neospinothalamic tract," "transduction," "transmission," "modulation," "perception," "A-delta fibers," "transient receptor potential vanilloid-1 ion channels (TRPV1)," "Cyclooxygenase (COX)," "5-lipoxygenase (5-LOX)," and "optogenetics" both individually and in combination. The primary focus of the selected studies was the neurophysiological dynamics of pain transmission and the key molecular alterations involved. Furthermore, this work aims to conduct a detailed examination of the mechanisms underlying the sensory-discriminative aspect of pain perception, with a specific focus on the unique role of the neospinothalamic tract. It is of significant importance to concretely express the neurophysiological signal transmission dynamics, especially the activation of A-delta fibers within the neuronal circuits forming the neospinothalamic tract and the specific synaptic interactions in the dorsal horn. Accordingly, the study aims to comprehensively elucidate the role of specific receptors, ion channels, and mediators involved in the regulation of these signal transmissions. This selective focus will enable a clearer identification of pharmacological and therapeutic targets for fast and localized pain transmission, an area gaining increasing importance in modern pain research.

A total of 380 references were identified during the initial search, and after removing 112 duplicate records retrieved across the different databases, 268 articles were screened at the title and abstract level. Studies that were not directly relevant to the core topic or lacked a sufficient neurophysiological and molecular foundation ($n = 114$) were excluded, leaving 154 references for full-text eligibility assessment. Following a detailed evaluation against criteria focusing on sensitization mechanisms, dual inhibition, and optogenetic neuromodulation, 50 studies were excluded due to a lack of experimental molecular or physiological data or target-specific mechanism analyses. Ultimately, 104 final references were included in this review to model and synthesize neospinothalamic pain mechanisms and their optogenetic regulation. The final literature search was performed on June 10, 2025 (Table 1).

3. Overview of the Pain Phenomenon

Pain, experienced as both an emotional and sensory process, can be defined as an unpleasant, life-quality-diminishing sensation and experience that is associated with actual or potential tissue damage.⁷ The experience of pain, which is influenced by both physical and psychological factors, is a phenomenon perceived through complex mechanisms generated by the peripheral nervous system, which are not yet fully elucidated.⁸ The stimulus, initiated by the receptor potential in nociceptors, travels through an electrophysiological flow to the dorsal horn of the posterior root ganglia, where it is modulated. The signals, having acquired a different characteristic through modulation, then arrive at the

thalamus and are finally evaluated in the upper brain centers, leading to the perception of pain.⁹

Table 1. Literature Selection Process

Flowchart State	Process Details	Number of References (n)
Identified references	Keyword search conducted via PubMed, Scopus, and Web of Science databases	380
Duplicate references	Elimination of duplicate articles retrieved from different databases	112
Screened references	Records screened at the title and abstract level with a focus on "pain," "neospinothalamic tract," "transduction," "transmission," "modulation," "perception," "A-delta fibers," "transient receptor potential vanilloid-1 ion channels (TRPV1)," "Cyclooxygenase (COX)," "5-lipoxygenase (5-LOX)," and "optogenetics"	268
Excluded references	Exclusion of studies not directly relevant to the topic or lacking adequate neurophysiological and molecular foundation	114
Eligible references	References retrieved for full-text assessment and evaluated according to "neospinothalamic tract," "pain," "sensitization mechanism", "dual inhibition", and "optogenetic neuromodulation" criteria	154
Ineligible references	Studies containing purely clinical observations rather than experimental molecular/physiological data or lacking target-specific mechanism analyses	50
Final references	Final number of references included in the review for the modeling and synthesis of neospinothalamic pain mechanisms and optogenetic regulation	104

The phenomenon of pain is a sensory and emotional process; besides being an aversive experience that impairs both physical and psychological well-being, it is also a harbinger of numerous dysfunctions.¹⁰ Neurons, neurotransmitters, and receptors concentrated in different brain regions, primarily the Ventral Tegmental Area (VTA) and the Nucleus Accumbens (NAc), play significant roles in pain perception. Furthermore, there are notable interconnections, especially neuronal networks, among the brain regions highlighted in pain perception.¹¹ Within the brain regions actively functioning in pain perception, excitation and inhibition mechanisms work in an integrated manner. Recent studies demonstrate that the regions involved in the perception of pain and other sensations acquire functional properties by forming complex connectivities.¹² It is believed that the cerebral cortex and the subcortical regions are the final destination of the pain-perceiving mechanisms through these connectivities.¹³

A compelling study regarding pain, which is an integrity formed by the connectivities among numerous neuronal, hormonal, molecular, and neurophysiological factors, has been conducted with nitric oxide (NO). The role of NO in pain perception, even though its mechanism is not yet fully understood, clearly highlights the importance of molecular investigation.¹⁴

The transmission of pain signals occurs via the neospinothalamic and paleospinothalamic tracts, which exhibit both anatomical and physiological differences.¹⁵ The Paleospinothalamic tract possesses an evolutionarily primitive characteristic. This tract transmits the emotional, autonomic, and general awareness dimensions of pain. These are typically slow, dull, and poorly localized types of pain.¹⁶ The Neospinothalamic tract has a highly developed structure and, unlike the paleospinothalamic tract, mediates the transmission of fast, sharp, and precisely localized pain sensations. The neospinothalamic tract is the main transmission system that provides projection to specialized sensory cortical areas.¹⁷

The neospinothalamic tract rapidly transmits the pain signal to the Ventral Posterior Lateral Nucleus (VPL) of the thalamus and then to the sensory cortex. This enables the

swift understanding of the exact location and character of the pain. The paleospinothalamic tract transmits the pain signal through complex pathways to the reticular formation, Periaqueductal Gray Matter (PAG), and the Medial Thalamic Nuclei (MDN). The painful stimulus is then relayed from these regions to the limbic system and the prefrontal cortex (Figure 1).

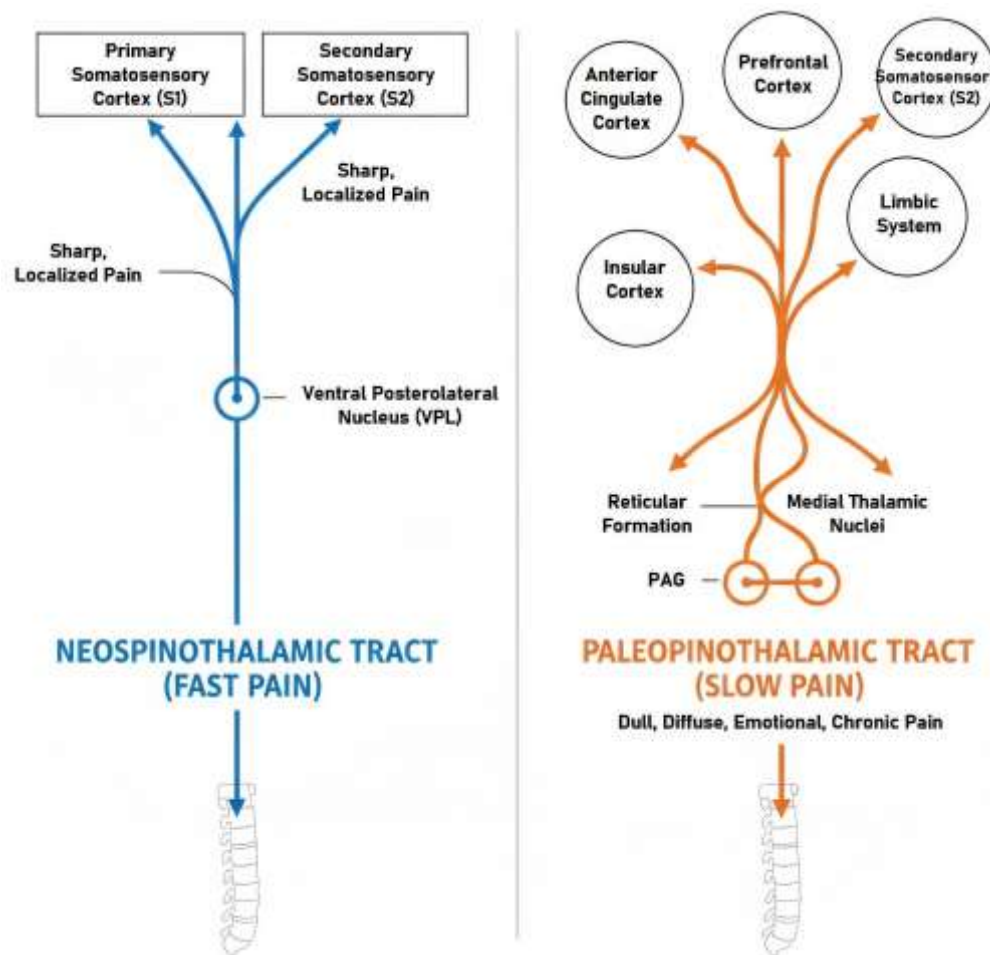


Figure 1. Comparison of the neospinothalamic and paleospinothalamic pathways

4. Nociceptors

Nociceptors are the pain receptors that generate stimuli via the necessary changes in receptor potential for activations referred to as nociception.¹⁸ Not all pain is attributable to physical factors; it can also arise psychologically. Therefore, not all pain originates through nociception, but every nociceptive process results in a pain response or experience. Pain resulting from nociception is inhibited by the supraspinal antinociceptive system (Figure 2).

Nociceptors are generally categorized into two groups based on the nerve fibers that innervate them: nociceptors innervated by A-delta fibers and those innervated by C-fibers. A-delta fibers receive mechanical and thermal stimuli that generate pain sensations, while C-fibers receive mechanical, thermal, and chemical stimuli, transmitting them up to the neocortex. Nociceptors innervated by C-fibers are called polymodal receptors because they respond to all three types of stimuli: mechanical, thermal, and chemical.¹⁹ Mechanical, thermal, and chemical stimuli that reach the upper regions of the Central Nervous System (CNS) are those that have been modulated in the spinal cord and are ready for evaluation in the cortex and various brain regions. There is a threshold value that must be exceeded for all stimuli to generate a pain sensation, and once this threshold is surpassed,

all stimuli acquire a noxious stimulus character.²⁰ Consequently, with the generation of the resulting depolarization wave, mechanical, thermal, and chemical stimuli are converted into electrical impulses. This conversion stage in pain perception is known as transduction. An example of transduction is the depolarization that occurs in nociceptors at a temperature of +43 °C with a thermal stimulus.²¹

The conversion of mechanical, thermal, and chemical stimuli into an electrical signal is a multifunctional mechanism. Here, the activation and inhibition reactions of important hormones and neuropeptides such as potassium, serotonin, bradykinin, histamine, prostaglandins, nerve growth factor (NGF), and substance P significantly contribute to this conversion.²²

There are many types of stimuli that alter the receptor potential of nociceptors found in the skin, joints, muscles, and visceral tissues.²³ Some nociceptors, which are surrounded by capillaries, muscle, and connective tissue, show sensitivity to only a single type of stimulus, while others show sensitivity to multiple, different types of stimuli.²⁴

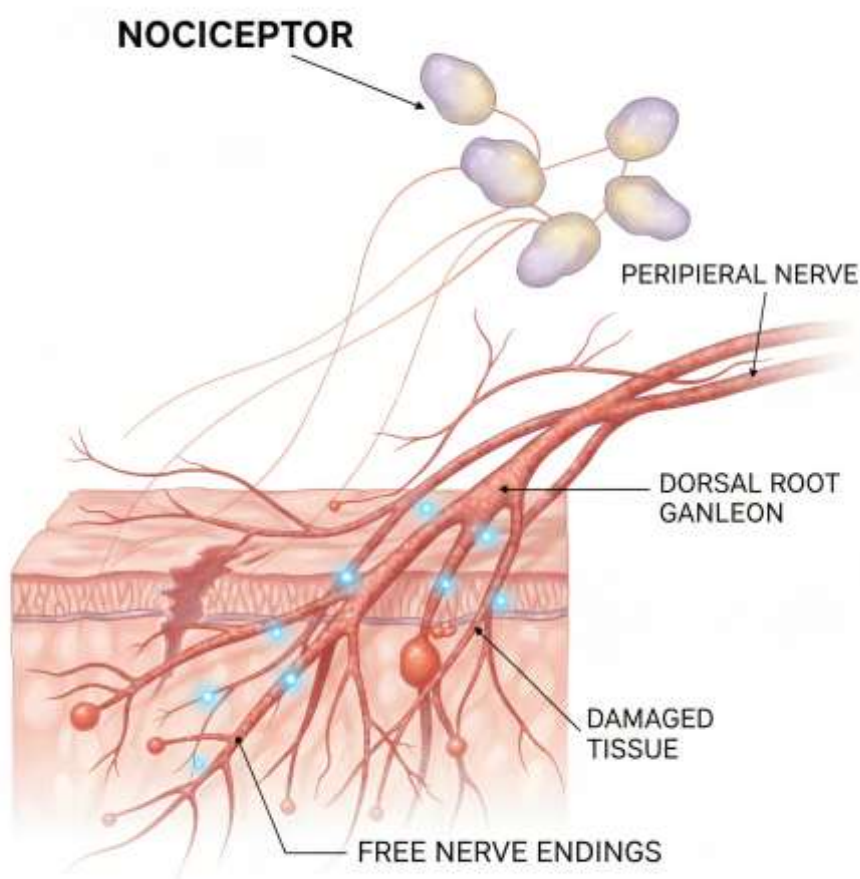


Figure 2. Nociceptors

5. Neurophysiology and Molecular Mechanism of Pain

The electrophysiological flow resulting from the change in receptor potential within nociceptors is transmitted to the neocortex via A-delta and C fibers and evaluated in regions that are not yet fully understood.²⁵ The unpleasant emotional and sensory responses resulting from this evaluation, which utilize these transmission pathways, constitute the general perspective of pain neurophysiology (Figure 3).

The transmission of pain signals to the upper brain centers occurs in four fundamental stages: transduction, transmission, modulation, and perception (Table 2).

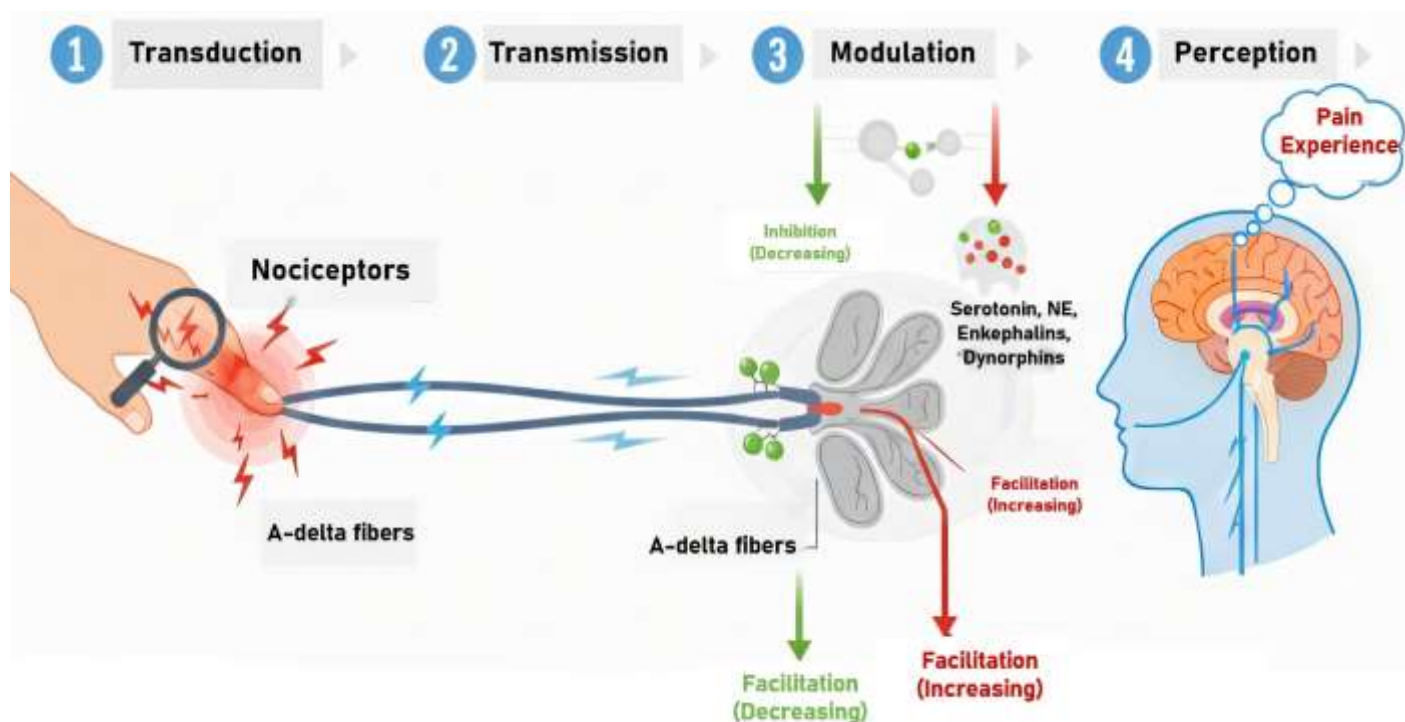


Figure 3. Stages of pain perception

5.1. Molecular Events in the Transduction Stage

Transduction is the stage where thermal, mechanical, and chemical stimuli, when delivered to nociceptors above the threshold value, are converted into an electrical signal.²⁶ The electrophysiological flow, generated by the formation of action potentials, is transmitted to the neocortex via afferent fibers.²⁷ Reactions occurring at the molecular level precede this electrophysiological flow; following trauma or a painful stimulus, there is an intense release of phospholipids.²⁸ The release of phospholipids activates arachidonic acid (AA), and the reactions become more sophisticated after this stage.²⁹

The release of 5-LOX and COX activates numerous mediators in pain reactions. In this respect, COX holds a more significant characteristic due to its activation of prostaglandins, which are short-distance messengers. Among the known types of prostaglandins, PGE₂ reaches the nociceptors, where it generates pain reactions and the electrophysiological flow (Table 3).

The pain signal, which originates during the transduction stage and acquires an electrophysiological nature, is transmitted via transmission to the neocortex, thalamus, and limbic system.³⁰ It should be clearly emphasized here that the mediators involved in pain reactions for the paleospinothalamic tract, which is evaluated in the brainstem and requires further study, may differ.³¹ The primary focus here is on the neospinothalamic tract in pain transmission, and this pathway contains two crucial types of fibers: fast pain fibers and slow pain fibers.³² The electrophysiological flow resulting from action potentials during the transduction stage, mechanical and thermal noxious stimuli are transmitted by fibers referred to as fast pain fibers or A-type fibers (specifically A-delta fibers), while chemical noxious stimuli are transmitted by the unmyelinated fibers referred to as slow pain fibers or C-type fibers.^{19,33} C-type fibers are unmyelinated and possess the ability to carry persistent mechanical and thermal noxious stimuli.³³

Cyclooxygenase Enzyme (COX): The two known forms of this enzyme are COX-1, the form expressed in normal cellular components, and COX-2, the form that emerges in inflamed cells.^{34,35} Nonsteroidal Anti-inflammatory Drugs (NSAIDs) typically achieve analgesia by inhibiting the COX-2 pathway. This enzyme, which is crucial for analgesia, is the primary element in the synthesis of prostaglandins during the transduction phase of pain generation.³⁴ Nuclear Factor kappa-B (NF-κB) ensures the synthesis and regulation of cytokines, adhesion molecules, and COX-2, which initiates pain, resulting from inflammation.³⁶

5-lipoxygenase Enzyme (5-LOX): 5-LOX acts as a pain trigger in many inflammatory and disease processes, affecting nociceptors via leukotrienes. It also plays important roles in the metabolism of AA and inflammatory fatty acids.³⁷ NSAIDs do not exhibit anti-activity against the 5-LOX enzyme; consequently, the formation of leukotrienes cannot be inhibited by this means.³⁸ Studies suggest that receptor antagonists of cysteinyl leukotrienes (cys-leukotrienes), which are activated by 5-LOX, exhibit an analgesic effect.^{39,40}

Arachidonic Acid Metabolism (AA): AA is produced in the cell membrane through the catalysis of phospholipase-A₂ acting on phospholipids and omega-6 fatty acids. The general mechanism of AA action occurs via 5-LOX, and therapeutic agents that act through dual inhibitory pathways on both 5-LOX and COX forms offer alternative treatment options.⁴¹ Prostaglandins activated by COX and leukotrienes activated by 5-LOX are believed to have complementary effects on pain. These two important pathways, present in pain generation (i.e., the activation of nociceptors' sensory pathways), act as fundamental mediators under the influence of AA.⁴²

Table 2. Physiological Stages and Molecular Mechanisms of Pain Transmission

Stage	Function	Localization	Molecular Mechanism
Transduction	Conversion of noxious stimuli (mechanical, thermal, chemical) into an electrical signal	Nociceptors	COX, 5-LOX, AA (Arachidonic Acid), Prostaglandins, Leukotrienes, TRPV1 Ion Channels
Transmission	Transmission of the electrical signal to the upper centers via afferent fibers	Primary Afferent Fibers (A-delta/C), Dorsal Horn (Lamina I/V), and Spinothalamic/Spino-cortical Tract	Substance P, Glutamate, Aspartate, Serotonin, Norepinephrine, Endogenous Opioids
Modulation	Assessment and alteration of the noxious stimulus in the spinal cord (excitation/inhibition)	Spinal Cord (Dorsal Horn), Brain Stem (PAG)	T-Cells, Substantia Gelatinosa (SG), Endogenous Opioids
Perception	Perception of the transmitted stimulus in the upper centers, experienced emotionally and sensorially	S-I and S-II, Thalamus (VPL/VPM), Limbic System (NAc, Amygdala)	Substance P, Neurokinin-A, Glutamate, Aspartate

In the transduction stage of pain sensation, mediator molecules such as prostaglandins and leukotrienes, released due to cell damage or inflammation, play a crucial role. The COX and 5-LOX enzymes, involved in the synthesis of these molecules, increase the peripheral sensitivity of nociceptors and lower the pain threshold. These molecular events have a complex relationship with the primary afferent fibers that are critical for signal transmission in the neospinothalamic tract.⁴³

5.1.1. A-delta Fibers

The effect of prostaglandins and leukotrienes on A-delta fibers, which form the basis of the neospinothalamic tract, is more limited compared to C fibers. A-delta fibers are associated with mechanical and thermal stimuli. The activation of these fibers primarily transmits fast and sharp pain. However, in conditions of severe inflammation, COX and 5-LOX products can indirectly lower the threshold of A-delta fibers as well, thereby intensifying fast pain transmission.⁴⁴

5.1.2. C-Fibers

Pro-inflammatory mediators, such as PGE₂ produced by the COX and 5-LOX enzymes, primarily activate receptors (like TRPV1) located at the terminals of C fibers. This activation leads to the generation of chronic or slow pain, resulting in an increase in signals originating from C fibers, which generally contribute to the paleospinothalamic tract, thereby causing chronic or persistent pain.⁴⁵ Consequently, although the COX and 5-LOX systems influence the sensitivity of both fiber types, they determine the initial intensity of the pain signal, particularly through their strong effects on C fibers. These signals subsequently diverge in the spinal cord into the neospinothalamic and paleospinothalamic tracts, forming both the fast-sensory and slow-emotional components of the pain experience.⁴⁶

Table 3. Molecules Involved in Pain Neurophysiology

Metabolic Pathway	Enzyme	Function	Role in Pain Mechanism	Target
COX Pathway	COX-2	PGE ₂ release	Lowers the nociceptor threshold, increasing sensitivity (Sensitization)	Gs-protein Coupled Receptors
5-LOX Pathway	5-LOX	Leukotriene release	Triggers neutrophil migration, enhances inflammation, and directly/indirectly activates nociceptors	Leukotriene Receptors
Combined COX and 5-LOX Pathway	PGE ₂	TRPV1 Ion Channel Modulation	Lowers the activation threshold of TRPV1 to thermal and chemical stimuli	TRPV1 Ion Channel

5.1.3. Role of TRPV Ion Channels in Transduction

The transient receptor potential vanilloid (TRPV) ion channels are of central importance in the detection of pain signals by primary afferent nociceptors. Among the members of the TRPV family, TRPV1 in particular is abundantly found at nociceptive terminals and initiates transduction by responding to thermal (above +43 °C), chemical (vanilloids like capsaicin), and acidic stimuli.⁴⁷ The activation of these channels triggers an influx of intracellular Ca⁺⁺ ions, thereby initiating depolarization and paving the way for the generation of an action potential. TRPV1 can also be modulated by pro-inflammatory mediators produced by the COX and 5-LOX enzymes. This modulation increases the channel's sensitivity, leading to a lowered pain threshold during inflammation. Although both the A-delta and C fibers involved in the neospinothalamic tract transmission express TRPV channels, due to the polymodal nociceptor nature of C fibers, TRPV1 channel activation plays a more dominant role in chemical and thermal pain transduction.⁴⁸

5.1.4. Molecular Relationship between Pungency and Thermal Sensation

Capsaicin, the main active ingredient in chili peppers, is not perceived solely as a chemical substance; it also activates the TRPV1 channel on nociceptors, thereby generating a physical sensation of heat. The TRPV1 channel is a polymodal receptor that responds to physical temperatures above +43 °C and to capsaicin.⁴⁹

5.2. Molecular Events in the Transmission Stage

The noxious stimuli, converted into an electrical signal, are transmitted to the upper centers via spinal afferent systems, with the active participation of A-delta and unmyelinated C-fibers.⁵⁰ Focusing more closely on this event, the electrophysiological flow and the changes within this flow, which naturally occur continuously in the neuronal systems established during the transduction stage, may play a role in the modulation stage.⁵¹ This mechanism has not yet been fully elucidated, but if evaluated from the perspective of the new scientific methodology of connectivity integrity, the synapse of A and C type fibers with the dorsal root ganglion triggers the release of numerous neurotransmitters and hormones.⁵² The most important known mediators among these are serotonin, norepinephrine, endogenous opioids, gamma-aminobutyric acid (GABA), somatostatin, and galanin.⁵³ It is noteworthy that endogenous opioids are also secreted, reacting or preparing for a reaction, during the process of pain generation.⁵⁴ The neospinothalamic tract is the most evolutionarily advanced pathway known; it largely projects to the thalamus and is then evaluated in yet-to-be-defined regions of the neocortex.⁵⁵ It is crucial to reiterate that the painful stimulus transmitted to the neocortex is transformed from what was generated in the transduction stage and is transmitted having acquired a new characteristic during the modulation stage.⁵⁶

Transmission, one of the four fundamental stages of pain signal conduction, is frequently used in the literature. To ensure definitional consistency, the transmission stage in painful stimulus conduction can be clarified in two main steps. The first step after transduction consists of primary afferent transmission.⁵⁷ In this stage, the generated action potential is conveyed via the primary afferent nociceptive fibers (A-delta and C fibers) to the dorsal horn of the spinal cord. This physiological process marks the initial entry of the painful stimulus or signal from the periphery into the central nervous system. The second step in pain signal transmission consists of the secondary afferent conduction system. This pathway is also referred to as the spinocortical transmission system. The actual transmission process involves the pain signal being received by T-neurons—which are the second-order neurons located in Lamina I and Lamina V of the dorsal horn—crossing the spinal cord, and projecting towards the thalamus and neocortex.⁵⁸

5.3. Molecular Events in the Modulation Stage

The modulation stage of pain neurophysiology is observed in both ascending and descending pathways.⁵⁹ Modulation in ascending pathways generally has a pain signal-enhancing role and is referred to as peripheral modulation. Modulation seen in descending pathways is called central modulation, where pain signals can be either amplified or attenuated.^{60,61}

5.3.1. Peripheral Modulation

Modulation is the process where a noxious stimulus is evaluated in the spinal cord and undergoes various changes before being transmitted to the upper centers.⁶² This stage of pain neurophysiology is closely associated with cognitive processes.⁶³ However, the mechanism of modulation is not fully understood, and various theories have been developed for it. The most important, and yet to be falsified, is the *Gate Control Theory*.⁶⁴ It is hypothesized that the impulse arriving at the spinal cord and dorsal horn is altered and modulated there, but there is no definitive molecular or neurophysiological evidence

regarding the exact pathways.⁶⁵ Specific subcortical structures and the brainstem are involved in the modulation stage—that is, in the temporary changes occurring in the neuronal structures and tissues of the spinal cord—and in the perception of the painful stimulus.⁶⁶

Gate Control Theory: In the posterior horn, there are groups of neurons, which are part of the sensory stimulus pathway, that are constantly inhibited. Noxious stimuli arriving via the A-delta fibers disrupt this inhibition.⁶⁷ These constantly inhibited groups of neurons are the Transmission cells (T-cells). When activated by a noxious stimulus, these cells enable the opening of the neurons in Lamina II and III, also known as the Substantia Gelatinosa (SG).⁶⁸ SG, which functions as an interneuron, is a component of the inhibition mechanisms during nociception processes.⁶⁹ SG and T-cells, the most crucial components of the gate control system, are located within the dorsal horn. Nerve fibers originating from nociceptors innervate these areas, allowing the transmission of noxious stimuli to the upper centers. According to the Gate Control Theory, the activation (opening) of SG is enabled by the activation of the constantly inhibited T-cells.⁷⁰ However, not all neural stimuli originating from nociceptors can remove the inhibition on T-cells and permit the opening of SG. Even if a stimulus occurs in the nociceptors, a certain threshold value must be exceeded for SG to open.⁷¹ Once the threshold value is surpassed, the constantly inhibitory signal pathways cease, and a different type of noxious stimulus is transformed into a new stimulus type and transmitted to the neocortex.⁷² SG activation is controlled by A-delta and C fibers, and the resulting stimulus, evaluated in the neocortex, is the outcome referred to as pain. It is believed that the descending pathways on the dorsal column from the supraspinal region also contribute to the modulation of the pain stimulus after the opening of SG. The Gate Control Theory explains the molecular and neurophysiological events occurring during the modulation phase of the pain perception process. Furthermore, this theory integrates and clarifies the previously proposed Pattern Theory and Specificity Theory.⁷³

A-delta and C-fibers carry pain signals, activating the T-cell and simultaneously inhibiting the SG interneuron. A-beta fibers carry non-painful touch or pressure signals. These fibers both excite the T-cell and activate the SG interneuron. The SG functions as a gate, applying constant inhibition on the T-cell. The T-cell is the main cell that transmits the pain signal to the CNS. The activation of this cell is modulated by the SG and the fiber inputs (Figure 4).

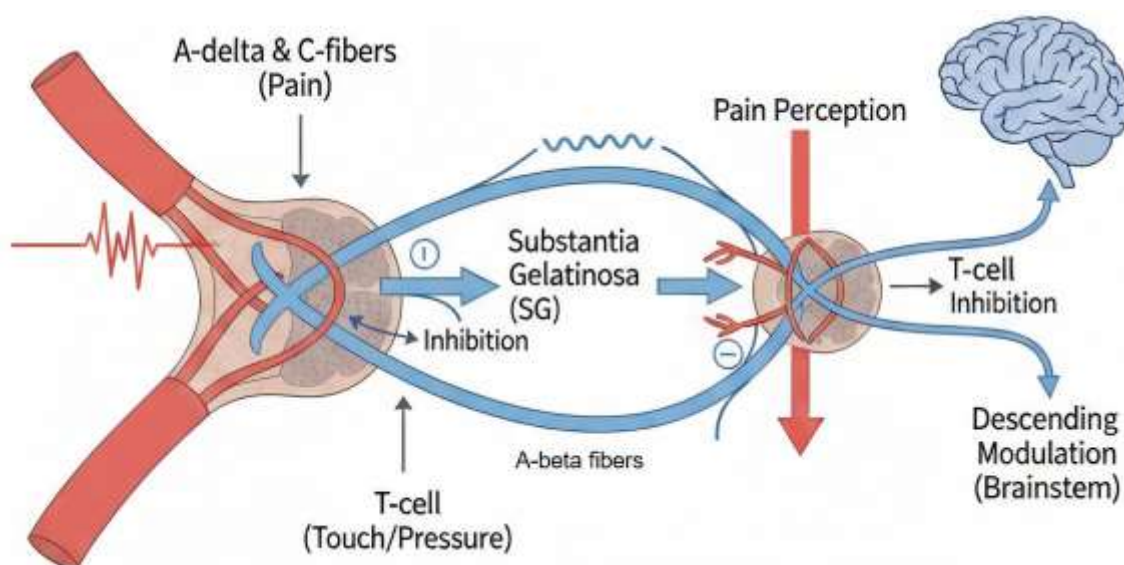


Figure 4. Gate Control Theory

5.3.2. Central Modulation

Central modulation occurs in the descending pain pathways. The descending pathways achieve modulation by directly influencing signal transmission in the dorsal horn of the spinal cord, using signals received from the brain's upper centers.⁷⁴ In this modulation, fibers descending from the PAG and RVM (Rostral Ventromedial Medulla) regions, primarily utilizing serotonin and norepinephrine, suppress pain transmission in the dorsal horn. However, neurons descending from the RVM can also release neurotransmitters that *increase* pain transmission. In this latter case, the neurons in the spinal cord become excessively activated and the pain signal is amplified.⁷⁵

5.3.3. Unexpected Effect of Descending Modulation Pathways: Placebo

The powerful analgesic response known as the Placebo effect in the brain is typically explained by the activation of descending antinociceptive pathways and the release of endogenous opioids. Pain reduction during the placebo effect is not merely a psychological change in perception; it is a genuine biochemical and neurophysiological event.⁷⁶

Functional Magnetic Resonance Imaging (fMRI) studies have shown that patients' expectations of reduced pain activate modulatory regions in the brainstem, such as the PAG, and that these regions descend to the dorsal horn to inhibit pain signal transmission.⁷⁷ PAG activation can be triggered not only by opioid drugs but also by a simple expectation. This finding proves the power of the modulation system and how fundamentally cognitive factors can alter the pain experience. Anatomically, this modulation begins in the PAG, located in the brainstem, and the nerve pathways originating from it constitute the main components of the descending pain control system. The PAG does not transmit the pain signal directly to the spinal cord but activates the RVM region located in the midline. Neurons in the RVM then descend to the dorsal horn of the spinal cord, where they perform synaptic modulation.⁷⁸

In the descending pathways, not only endogenous opioids but also monoamine neurotransmitters like serotonin (5-HT) and norepinephrine (NE) play a critical role.⁷⁹ The pathways descending from the RVM increase neurotransmitter release in the dorsal horn, the junction point between nociceptive primary afferent neurons and secondary neurons in the spinal cord. These chemicals inhibit the upward transmission of the pain signal towards the thalamus at both the presynaptic and postsynaptic levels, primarily through inhibitory interneurons in the spinal cord.⁸⁰

The endogenous opioids underlying placebo analgesia are neuropeptides such as enkephalins, endorphins, and dynorphins. These neuropeptides bind to μ -opioid receptors (MOR), which are highly concentrated on nociceptive nerve terminals and interneurons in the dorsal horn.⁸¹ MOR activation hyperpolarizes neuronal membranes, reducing neuronal excitability, and thus strongly suppressing pain signal transmission. This mechanism is biochemically identical to the analgesia provided by exogenous opioid drugs like morphine and fentanyl.⁸²

5.4. Neurological Events Occurring in the Perception Stage

This is the stage where the impulse transmitted from the spinal cord via the nociceptive afferent pathways is conveyed to and perceived by the CNS.⁸³ Fibers of the neospinothalamic tract reach the ventroposterolateral (VPL) and ventroposteromedial (VPM) nuclei in the thalamus, and from there, they project to the primary and secondary somatosensory cortices (S-I and S-II). This projection is the main mechanism that allows the perception of the pain's fast, sharp nature and precise localization. The contributions of neuronal activations and the released Substance P, Neurokinin-A, Glutamate, and Aspartate are known in this perception process.⁸⁴ The crucial point to emphasize in the pain perception process is that a single brain region is not responsible for perception; stimuli crossing through the thalamus are perceived via the connectivities of the neocortex, NAc

(Nucleus Accumbens), amygdala, and various parts of the limbic system.⁸⁵ It is worth reiterating that the stimuli arriving here are those that have been altered and rendered perceptible during the modulation stage in the spinal cord. From the perspective of the scientific methodology known as connectivity integrity, pain perception—or the perception stage—constitutes the entirety of this process.⁸⁶ This entirety is formed by connectivities such as neuronal connections in different brain regions, their consolidation, and the activation and/or inhibition of neurotransmitter pathways.⁸⁷

In the perception phase, pain is experienced emotionally and physically, while also inducing striking changes in the neurophysiological flow.⁸⁸ The fundamental mechanisms of perception emerge as a result of intervention in this flow, which leads to the conclusion that pain is also a psychological phenomenon.⁸⁹ For this reason, when classifying pain, an interesting type of pain called phantom limb pain is often mentioned. Phantom limb pain can be briefly concretized with the following example: a person who has lost a leg may feel pain as if the leg were still there.⁹⁰ This is due not only to psychological factors but also to physiological processes that are yet to be fully explained. Since the brain does not have an experience to understand the presence of organs, this may be one of the significant causes of phantom pain.⁹¹ However, not only the brain but also different subcortical regions may contribute to the perception stage.⁹² Because pain is a stimulatory feature that initiates primitive drives such as avoidance, protection, fighting, and feeding, it is important to consider that primitive neuronal regions operating in the brainstem, in addition to components like the neocortex, NAc, amygdala, and hippocampus, also play a role in pain perception.⁹³ The perception stage gains meaning through the projection provided by the neospinothalamic tract to the upper brain centers, representing the final point where the sensory-discriminative components of the pain experience are evaluated.⁹⁴

5.4.1. Phantom Pain and the Pain Neuromatrix

The final perception of signals transmitted by the neospinothalamic tract is one of the most complex processes in the brain. The most striking proof that pain is not merely a sensory experience but also a cognitive and emotional output is the phenomenon of Phantom Limb Pain (PLP).⁹⁵ PLP is the condition, observed in 60%-80% of amputees, where a severe and realistic sensation of pain is experienced despite the physical absence of the limb. This condition, which indicates that pain is not a simple signal transmission, is explained by the "Neuromatrix Theory" proposed by Ronald Melzack.⁹⁶ According to this theory, a broad neural network composed of different brain regions (thalamus, limbic system, S-I/S-II) continuously produces an output regarding the body's integrity (the neuromatrix signature). Even when the limb is lost, this matrix remains active and can generate a pain output without a pain signal input. This demonstrates that pain is actually a perception constructed in the brain and that the connectivities of the neospinothalamic tract in the cortex can be triggered independently of true physical input.⁹⁷

5.5. Novel Experimental Method for Precise Control of Pain Mechanisms

The neospinothalamic tract and its sensitization mechanisms (the COX/5-LOX and TRPV1 axis), which are the focus of this review examining the neurophysiological dynamics and molecular basis of pain perception, can be analyzed more precisely using optogenetic techniques. This approach facilitates the development of new therapeutic strategies for pain in the future.⁹⁸

5.5.1. Optogenetics

Optogenetics is a biological method formed by the combination of genetic and optical strategies that allow the control of cellular activities, particularly the efficacy of neurons, using light.⁹⁹ Etymologically, the term merges "optic" (light) and "genetic" (gene-derived)

elements. This method is a neuromodulation approach used to monitor and direct neural activity in living tissues and cells.¹⁰⁰

The fundamental principle of the technique involves transferring the genes of light-sensitive proteins called opsins, derived from bacteria or algae, into the target neurons via a harmless viral vector.¹⁰¹ Opsins are genes that enable the formation of light-responsive ion channels that embed in the neuronal membrane, namely channelrhodopsin (ChR) and halorhodopsin (NpHR) (Figure 5).

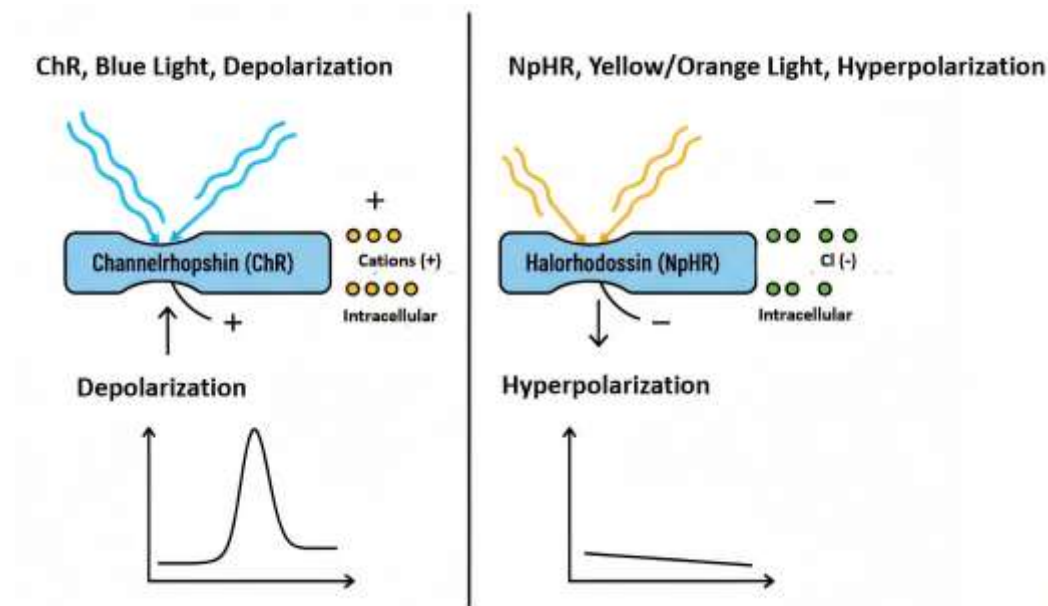


Figure 5. The ChR and NpHR channels generated by the opsin gene

ChR, which is activated by blue light, allows the influx of cations into the cell, leading to depolarization. NpHR, which is typically sensitive to orange/yellow light, pumps chloride ions into the cell, generating hyperpolarization (Figure 6).

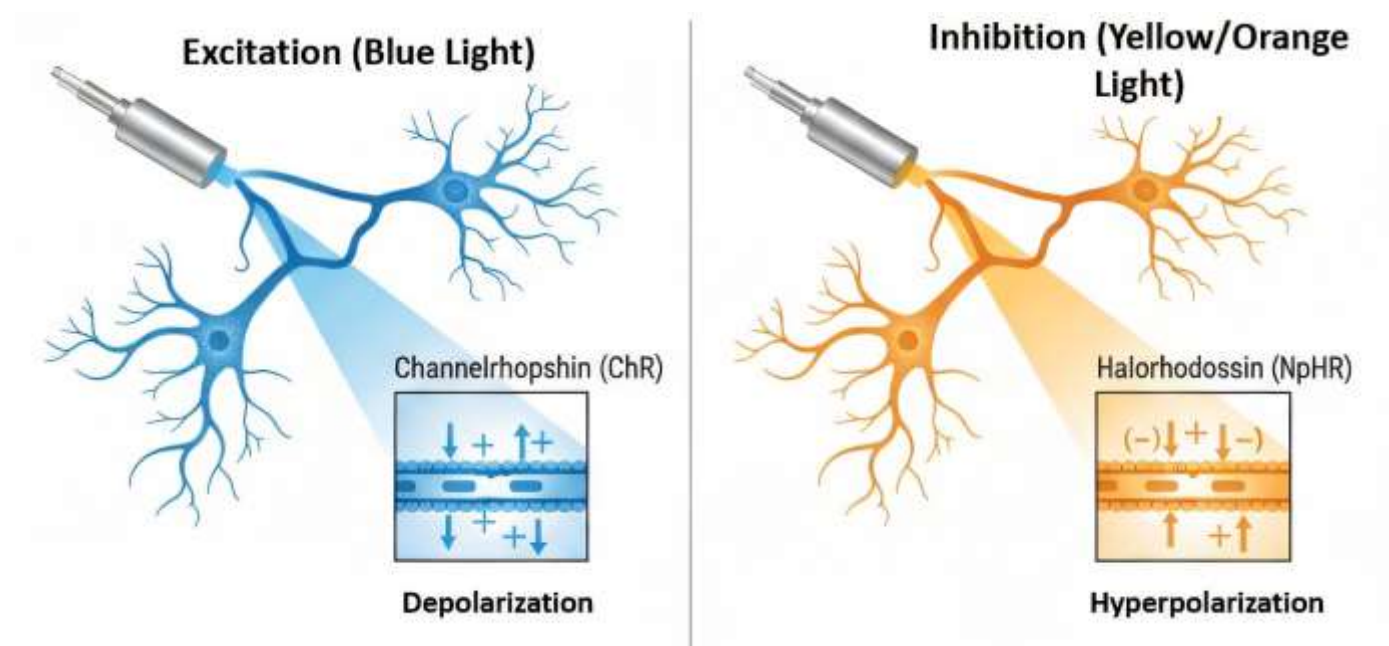


Figure 6. Effects of blue and yellow light on ChR-NpHR channels

In the optogenetic experimental method, excitation or inhibition can be achieved reversibly with millisecond precision by delivering light of a specific wavelength to the target neuronal population via optic fibers. Thanks to this high temporal and spatial resolution, optogenetics offers significant potential in elucidating the functioning of the complex neuronal mechanisms involved in pain transmission (Figure 7).

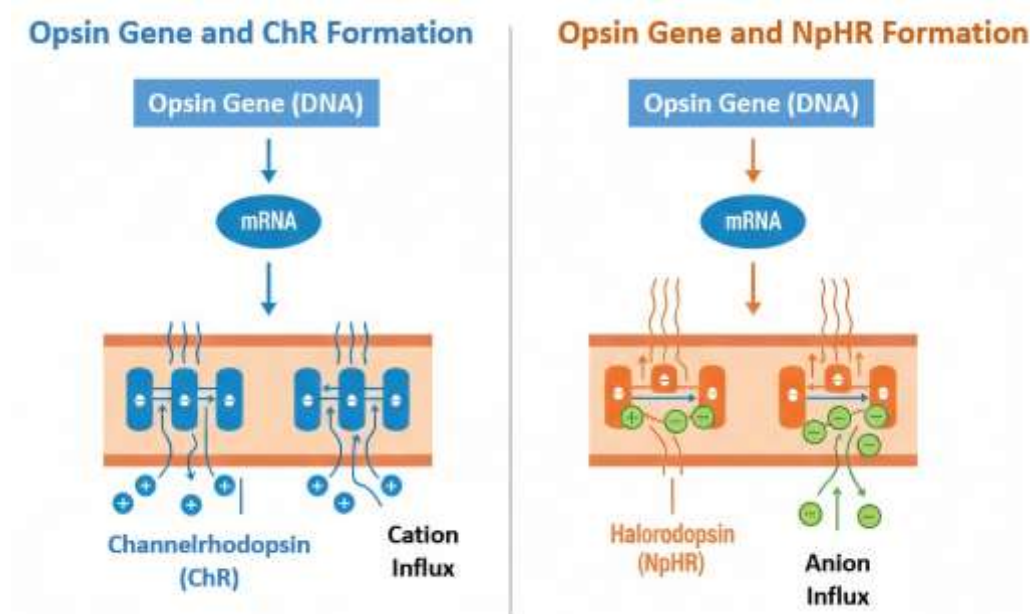


Figure 7. Excitation mechanism of the ChR channel and inhibition mechanism of the NpHR channel

5.5.2. Optogenetic Applications in the Axis of Transduction and Molecular Sensitization

The optogenetic experimental method can be utilized to mimic or control the cellular effects of molecular events occurring during the transduction stage of pain perception.¹⁰²

Investigation of Nociceptor Activation

Opsin genes restricted to the TRPV1 gene promoter can be introduced specifically into the A-delta fiber populations (transmitting fast pain) and C-fiber populations (transmitting slow pain). This strategy allows for the precise triggering or inhibition of neuronal activation using light alone, without altering the intrinsic threshold of the primary afferent neurons or relying on COX/5-LOX products (Figure 8).

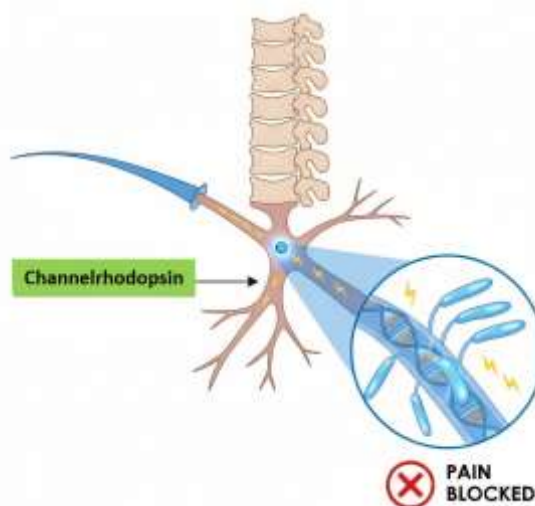


Figure 8. Activation of nociceptors with blue light

Mimicking TRPV1 Modulation

The Ca^{++} influx and subsequent action potential formation caused by TRPV1 activation can be mimicked optogenetically using ChR. This allows for the neurophysiological consequences of the COX and 5-LOX products' effect on increasing TRPV1 sensitivity to be modeled with light. Consequently, it enables the analysis of the electrical signal conversion (transduction) underlying sensitization (Figure 9).

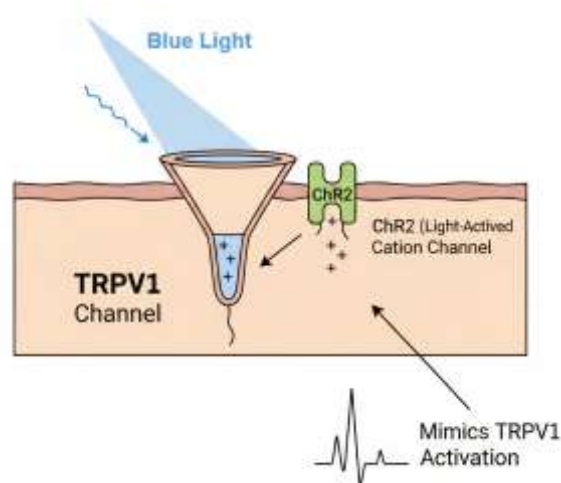


Figure 9. Optogenetic mimicry of TRPV1 modulation

5.5.3. Applications in the Axis of Neospinothalamic Transmission and Modulation

The complex mechanisms of the neospinothalamic tract, which ensures the transmission of the pain signal from the spinal cord to the thalamus and cortex, can be mapped and modulated using the optogenetic method.¹⁰³

Elucidation of the Gate Control Theory

The modulation stage occurring in the dorsal horn and the Gate Control Theory involve the interaction of neurons that transmit and inhibit noxious stimuli (e.g., T-cells). Optogenetics can clearly demonstrate how the pain gate opens and closes *in vivo* by selectively activating or inhibiting the specific neurons within these excitation/inhibition circuits using light (Figure 10).

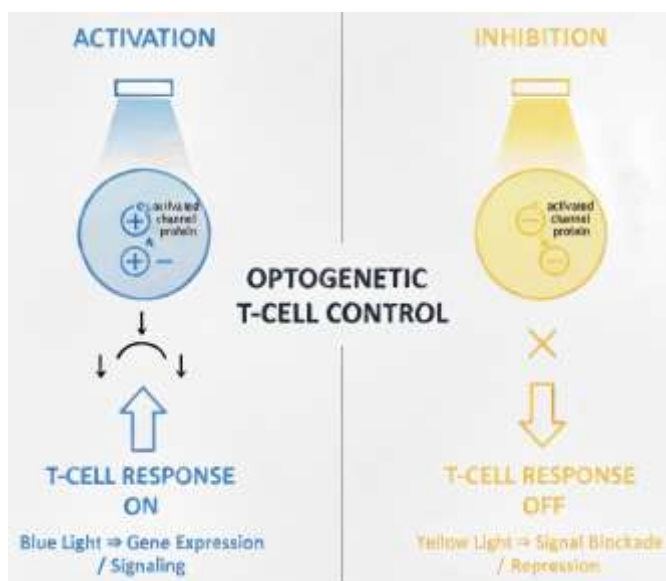


Figure 10. Effect of blue and yellow light on T-cells

Control of Supraspinal Pathways

Studies on the upper centers where pain is perceived and on the descending antinociceptive pathways can be advanced using optogenetics. Targeting the neuronal populations in these regions with light allows for the modeling of the signal's effects on emotional and sensory responses before or after the signal reaches the perception stage (Figure 11).

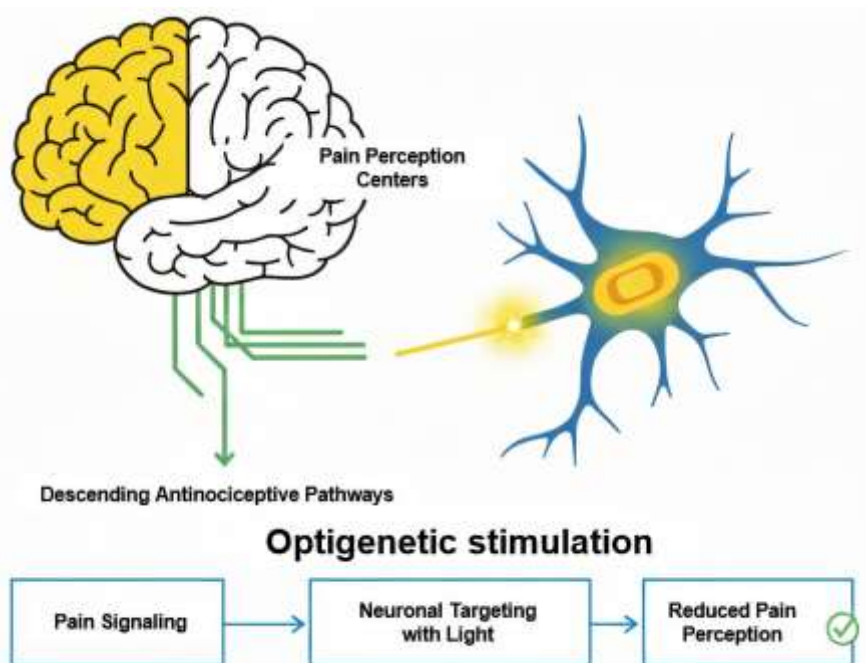


Figure 11. Role of yellow light in supraspinal pathways

5.5.4. Therapeutic Potential of Optogenetics

The limitations of current pharmacological approaches stem from targeting a single molecular mechanism (e.g., only COX-2 or only TRPV1). Optogenetics holds the potential to revolutionize the development of next-generation therapies by overcoming these limitations.¹⁰⁴

Unlike conventional drugs, optogenetics can minimize systemic side effects by targeting only the specific neurons that transmit the pathological pain signal. Furthermore, through customized neuromodulation, pathologically activated circuits in chronic pain conditions (e.g., in the spinal cord or the thalamocortical pathway) can be silenced using light delivered via implanted optical devices. This approach paves the way for future gene-based neuromodulation treatments involving the direct control of neural activity, complementing molecular targets such as dual inhibitors and TRPV1 antagonists (Figure 12).

6. Conclusion

This review highlights the critical role of the neospinothalamic pathway and its molecular sensitization mechanisms in fast, localized pain processing. Key molecular players at the transduction level—specifically COX-2, 5-LOX, and TRPV1 ion channels—collectively drive peripheral sensitization. While traditional analgesics primarily target single pathways, current preclinical literature suggests that dual COX/5-LOX inhibition, potentially combined with TRPV1 modulation, may offer a more comprehensive approach to reducing inflammatory nociceptive drive. However, further translational research and rigorous clinical trials are required to establish the safety, optimal dosing, and actual

clinical efficacy of these multi-target pharmacological strategies. In parallel, optogenetics serves as a powerful experimental tool with high temporal and spatial resolution to decipher specific neuronal circuits within the neospinothalamic tract and dorsal horn networks. Although light-based neuromodulation demonstrates significant potential in pre-clinical models for silencing pathologically active pain pathways, its clinical translational utility remains limited by challenges in gene delivery, optical hardware implantation, and long-term biocompatibility. Future investigations should therefore focus on bridging these methodological gaps to carefully assess the realistic therapeutic scope of target-specific neuromodulation in chronic pain management.

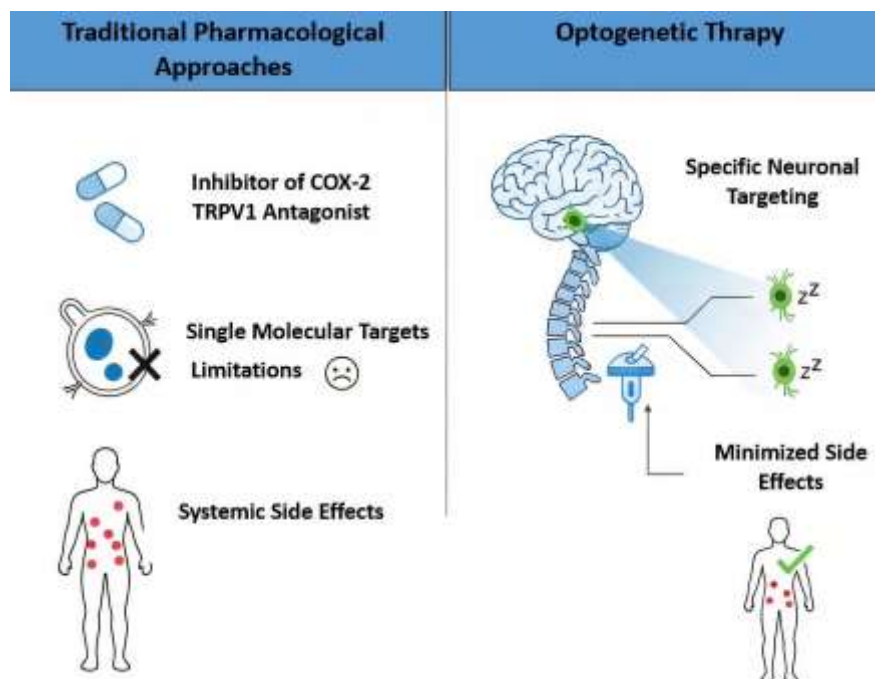


Figure 12. Comparison of Traditional and Optogenetic Treatment Approaches in Pain Therapy

Conflict of interest statement: There is no conflict of interest among the authors.

Authors contributions: TB: Conceptualization; Data curation; Investigation; Methodology; Validation; Visualization; Writing-original draft; Writing- review & editing. MS: Validation; Writing-original draft; Critics

References

- Świeboda P, Filip R, Prystupa A, Drozd M. Assessment of pain, types, mechanism.pdf. *Ann Agric Env Med*. 2013;20(1):2-7. <https://www.aaem.pl/Assessment-of-pain-types-mechanism-and-treatment,106177,0,2.html>
- Woolf CJ. Central sensitization: Implications for the diagnosis and treatment of pain. *Pain*. 2011;152(3):1-31. doi:10.1016/j.pain.2010.09.030.
- Ghatak S, Vyas A, Misra S, et al. Novel di-tertiary-butyl phenylhydrazones as dual cyclooxygenase-2/5- lipoxygenase inhibitors: Synthesis, COX/LOX inhibition, molecular modeling, and insights into their cytotoxicities. *Bioorganic Med Chem Lett*. 2014;24(1):317-324. doi:10.1016/j.bmcl.2013.11.015
- Pamplona FA, Menezes-de-Lima O, Takahashi RN. Aspirin-triggered lipoxin induces CB1-dependent catalepsy in mice. *Neurosci Lett*. 2010;470(1):33-37. doi:10.1016/j.neulet.2009.12.050
- Park HJ, Moon DE. Pharmacologic Management of Chronic Pain. *Korean J Pain*. 2010;23(June):99-108. doi:10.1016/j.gtc.2010.08.001

6. Espinosa-Juárez JV, Chiquete E, Estañol B, Aceves J de J. Optogenetic and Chemogenic Control of Pain Signaling: Molecular Markers. *Int J Mol Sci.* 2023;24(12):1-16. doi:10.3390/ijms241210220
7. Hannibal KE, Bishop MD. Chronic stress, cortisol dysfunction, and pain: A psychoneuroendocrine rationale for stress management in pain rehabilitation. *Phys Ther.* 2014;94(12):1816-1825. doi:10.2522/ptj.20130597
8. Dubin AE, Patapoutian A. Nociceptors: The sensors of the pain pathway. *J Clin Invest.* 2010;120(11):3760-3772. doi:10.1172/JCI42843
9. Todorovic SM, Jevtovic-Todorovic V. Regulation of T-type calcium channels in the peripheral pain pathway. *Channels.* 2007;1(4):238-245. doi:10.4161/chan.4953
10. Saito N, Shima R, Yamada Y, Nagaoka M, Ito E, Yoshioka T. A Proposed Molecular Mechanism for Physical Analgesia in Chronic Pain. *Neural Plast.* 2018;2018. doi:10.1155/2018/1260285
11. Haghparsat A, Azhdari-Zarmehri H, Reisi Z, Vaziri A, Haghparsat A, Shaigani P. Involvement of orexin-2 receptors in the ventral tegmental area and nucleus accumbens in the antinociception induced by the lateral hypothalamus stimulation in rats. *Peptides.* 2013;47:94-98. doi:10.1016/j.peptides.2013.07.012
12. Altun A, Yildirim K, Ozdemir E, Bagcivan I, Gursoy S, Durmus N. Attenuation of morphine antinociceptive tolerance by cannabinoid CB1 and CB2 receptor antagonists. *J Physiol Sci.* 2015;65(5):407-415. doi:10.1007/s12576-015-0379-2
13. Argoff CE, Albrecht P, Irving G, Rice F. Multimodal analgesia for chronic pain: Rationale and future directions. *Pain Med.* 2009;10(SUPPL. 2). doi:10.1111/j.1526-4637.2009.00669.x
14. Ignorro L. NO İle Kalp Hastalıklarına Son. Özbay Yayıncılık; 2007.
15. Karcz M, Abd-elsayed A, Chakravarthy K, et al. Pathophysiology of Pain and Mechanisms of Neuromodulation : A Narrative Review (A Neuron Project). *J Pain Res.* 2024;17:3757-3790.
16. Rashmi BR, Ebrahim NKC. A review on pain and its signals modulation by body. *Int J Compr Adv Pharmacol.* 2019;4(3):84-90.
17. Gonzalez-Hermosillo DC, Gonzalez-Hermosillo LM, Villaseñor-Almaraz M, et al. Current Concepts of Pain Pathways: A Brief Review of Anatomy, Physiology, and Medical Imaging. *Curr Med Imaging.* 2024;20:1-17. doi:10.2174/1573405620666230519144112
18. Yang D, Jacobson A, Meerschaert KA, et al. Nociceptor neurons direct goblet cells via a CGRP-RAMP1 axis to drive mucus production and gut barrier protection. *Cell.* 2022;185(22):4190-4205.e25. doi:10.1016/j.cell.2022.09.024
19. Lefaucheur JP. *Clinical Neurophysiology of Pain.* Vol 161. 1st ed. Elsevier B.V.; 2019. doi:10.1016/B978-0-444-64142-7.00045-X
20. Bell A. The neurobiology of acute pain. *Vet J.* 2018;237:55-62. doi:10.1016/j.tvjl.2018.05.004
21. Cohen SP, Mao J. Neuropathic pain: Mechanisms and their clinical implications. *BMJ.* 2014;348:1-12. doi:10.1136/bmj.f7656
22. Mertens P, Blond S, David R, Rigoard P. Anatomy, physiology and neurobiology of the nociception: A focus on low back pain (part A). *Neurochirurgie.* 2015;61(S1):S22-S34. doi:10.1016/j.neuchi.2014.09.001
23. Middleton SJ, Barry AM, Comini M, et al. Studying human nociceptors: From fundamentals to clinic. *Brain.* 2021;144(5):1312-1335. doi:10.1093/brain/awab048
24. Welters ID, Menzebach A, Goumon Y, et al. Morphine inhibits AP-1 activity and CD14 expression in leukocytes by a nitric oxide and opioid receptor-dependent mechanism. *Eur J Anaesthesiol.* 2007;24(11):958-965. doi:10.1017/S026502150700083X
25. Robert Cronin Yung Peng, Rose Khavari ND. Select noxious stimuli induce changes on corneal nerve morphology. *Physiol Behav.* 2017;176(3):139-148. doi:10.1159/000444169.Carotid
26. Russo MM, Sundaramurthi T. An Overview of Cancer Pain: Epidemiology and Pathophysiology. *Semin Oncol Nurs.* 2019;35(3):223-228. doi:10.1016/j.soncn.2019.04.002
27. Ong WY, Stohler CS, Herr DR. Role of the Prefrontal Cortex in Pain Processing. *Mol Neurobiol.* 2019;56(2):1137-1166. doi:10.1007/s12035-018-1130-9
28. Possomato-Vieira, José S. and Khalil RAK, Modeling O 2. O. ESE and S. Phospholipase A2 Inhibitor-Loaded Phospholipid Micelles Abolish Neuropathic Pain. *Physiol Behav.* 2017;176(12):139-148. doi:10.1021/acs.nano.0c00999.Additional
29. Oehler B, Brack A, Blum R, Rittner HL. Pain Control by Targeting Oxidized Phospholipids: Functions, Mechanisms, Perspectives. *Front Endocrinol (Lausanne).* 2021;11(January):1-9. doi:10.3389/fendo.2020.613868
30. Lee GI, Neumeister MW. Pain: Pathways and Physiology. *Clin Plast Surg.* 2020;47(2):173-180. doi:10.1016/j.cps.2019.11.001
31. Bourne S, Machado AG, Nagel SJ. Basic anatomy and physiology of pain pathways. *Neurosurg Clin N Am.* 2014;25(4):629-638. doi:10.1016/j.nec.2014.06.001
32. Duan WR, Xie YK. Modulation of C-nociceptive activities by inputs from myelinated fibers. *Adv Exp Med Biol.* 2016;904:33-40. doi:10.1007/978-94-017-7537-3_3

33. Sopacua M, Hoeijmakers JGJ, Merckies ISJ, Lauria G, Waxman SG, Faber CG. Small-fiber neuropathy: Expanding the clinical pain universe. *J Peripher Nerv Syst.* 2019;24(1):19-33. doi:10.1111/jns.12298
34. Cashman JN. The mechanisms of action of NSAIDs in analgesia. *Drugs.* 1996;52(SUPPL. 5):13-23. doi:10.2165/00003495-199600525-00004
35. Baser T. Ghrelin ve Oreksin Reseptör Agonistlerinin Morfin Analjezisi ve Toleransı Üzerine Etkileri. Sivas Cumhuriyet Üniversitesi; 2018.
36. Peng SY, Liu Y, Bao XH, et al. Inhibition of 5-lipoxygenase and cyclooxygenase-2 pathways by pain-relieving plaster in macrophages. *Pharm Biol.* 2011;49(7):716-726. doi:10.3109/13880209.2010.544043
37. Burnett BP, Levy RM. 5-Lipoxygenase metabolic contributions to NSAID-induced organ toxicity. *Adv Ther.* 2012;29(2):79-98. doi:10.1007/s12325-011-0100-7
38. Bjordal JM, Ljunggren AE, Klovning A, Slørdal L. Non-steroidal anti-inflammatory drugs, including cyclo-oxygenase-2 inhibitors, in osteoarthritic knee pain: Meta-analysis of randomised placebo controlled trials. *Br Med J.* 2004;329(7478):1317-1320. doi:10.1136/bmj.38273.626655.63
39. Cortes-Burgos LA, Zweifel BS, Settle SL, et al. CJ-13610, an orally active inhibitor of 5-lipoxygenase is efficacious in preclinical models of pain. *Eur J Pharmacol.* 2009;617(1-3):59-67. doi:10.1016/j.ejphar.2009.06.058
40. Kanjhan R. Opioids and Pain. *Clin Exp Pharmacol Physiol.* 1995;22(6-7):397-403. doi:10.1111/j.1440-1681.1995.tb02029.x
41. Meshram MA, Bhise UO, Makhal PN, Kaki VR. Synthetically-tailored and nature-derived dual COX-2/5-LOX inhibitors: Structural aspects and SAR. *Eur J Med Chem.* 2021;225:113804. doi:10.1016/j.ejmech.2021.113804
42. Metkin G, Süntar İ, Şenol Deniz FS, Tugay O, Demiralp M, Pittalà V. Investigating COX-2 and 5-LOX Enzyme-Related Anti-Inflammatory and Antioxidant Activities and Phytochemical Features of *Scutellaria salviifolia* Benth. *Int J Mol Sci.* 2025;26(12):1-17. doi:10.3390/ijms26125608
43. Xie L, Lee DY wei, Shang Y, et al. Phytomedicine Characterization of spirostanol glycosides and furostanol glycosides from *anemarrhenae rhizoma* as dual targeted inhibitors of 5-lipoxygenase and Cyclooxygenase-2 by employing a combination of affinity ultra filtration and HPLC / MS. *Phytomedicine.* 2020;77:1-10. doi:10.1016/j.phymed.2020.153284
44. Ji G, Zhou S, MY K, Westlund K, Carlton S. Plasticity in Intact Aδ- and C-Fibers Contributes to Cold Hypersensitivity in Neuropathic Rats. *Neuroscience.* 2008;150(1):182-193.
45. Kawabata A. Lipid Mediators and Pain Signaling Prostaglandin E 2 and Pain — An Update. *Biol Pharm Bull* 34(8). 2011;34(8):1170-1173.
46. Basbaum A. History of Spinal Cord “ Pain ” Pathways Including the Pathways Not Taken. *Front Pain Res.* 2022;3:1-6. doi:10.3389/fpain.2022.910954
47. Premkumar LS, Sikand P. TRPV1 : A Target for Next Generation Analgesics. *Curr Neuropharmacol.* 2008;6:151-163.
48. Zhang X, Li L, McNaughton PA. Proinflammatory Mediators Modulate the Heat-Activated Ion Channel TRPV1 via the Scaffolding Protein AKAP79 / 150. *Neuron.* 2008;(59):450-461. doi:10.1016/j.neuron.2008.05.015
49. Darre L, Domene C. Binding of Capsaicin to the TRPV1 Ion Channel. *Mol Pharm.* 2015;(12):4454-4465. doi:10.1021/acs.molpharmaceut.5b00641
50. Crofford LJ. Chronic Pain: Where the Body Meets the Brain. *Trans Am Clin Climatol Assoc.* 2015;126:167-183.
51. Kitahata LM. Pain pathways and transmission. *Yale J Biol Med.* 1993;66(5):437-442.
52. Argoff C. Mechanisms of pain transmission and pharmacologic management. *Curr Med Res Opin.* 2011;27(10):2019-2031. doi:10.1185/03007995.2011.614934
53. Maio G Di, Villano I, Ilardi CR, et al. Mechanisms of Transmission and Processing of Pain: A Narrative Review. *Int J Environ Res Public Health.* 2023;20(4). doi:10.3390/ijerph20043064
54. Kağan Yücel R, Özdemir F, Ural Ulucan H, Hizli Yücel S. Endogenous opioid system in pain management: Mechanisms, influences, and clinical implications. *J Exp Clin Med.* 2025;42(2):207-211. doi:10.52142/omujecm.42.2.15
55. Kaye AD, Urman RD, Vadivelu N. Essentials of Regional Anesthesia.; 2012. doi:10.1007/978-1-4614-1013-3
56. Xie YF, Wang J, Bonin RP. Optogenetic exploration and modulation of pain processing. *Exp Neurol.* 2018;306(April):117-121. doi:10.1016/j.expneurol.2018.05.003
57. Yağcı Ü, Saygın M. Ağrı fizyopatolojisi. *Med J SDU.* 2019;26(2):209-220. doi:10.17343/sdutfd.444237
58. Willis W, Westlund K. Neuroanatomy of the Pain System and of the Pathways That Modulate Pain. *J Clin Neurophysiol.* 2021;14(1):2-31. doi:10.1097/00004691-199701000-00002.Neuroanatomy
59. Cross SA. Pathophysiology of Pain. *Mayo Clin Proc.* 1994;69(4):375-383. doi:10.1016/S0025-6196(12)62225-3

60. Bodnar R, Heinricher MM. Central Mechanisms of Pain Modulation. *Curr Opin Neurobiol.* 1999;9:436-441. doi:10.1007/978-3-030-88832-9_102
61. Liu D, Hu SW, Wang D, et al. An Ascending Excitatory Circuit from the Dorsal Raphe for Sensory Modulation of Pain. *J Neurosci.* 2024;44(4):1-21. doi:10.1523/JNEUROSCI.0869-23.2023
62. Mwendwa. Mechanisms and Pathways of Pain Photobiomodulation: A Narrative Review. *Physiol Behav.* 2019;176(3):139-148. doi:10.1016/j.jpain.2021.02.005.Mechanisms
63. Leung RH, Stroman PW. Neural correlates of cognitive modulation of pain perception in the human brainstem and cervical spinal cord using functional magnetic resonance imaging: A review. *Crit Rev Biomed Eng.* 2016;44(1-2):33-45. doi:10.1615/CritRevBiomedEng.2016016540
64. Justin I. Odegaard, Chawla A. Constructing and Deconstructing the Gate Theory of Pain Lorne. Bone. 2008;23(1):1-7. doi:10.1016/j.pain.2013.12.010.Constructing
65. Congress I. The gate control theory of pain. *Br Med J.* 1978;2(6137):586-587. doi:10.1136/bmj.2.6137.586-a
66. Bingel U, Tracey I. Imaging CNS modulation of pain in humans. *Physiology.* 2008;23(6):371-380. doi:10.1152/physiol.00024.2008
67. Braz J, Solorzano C, Wang X, Basbaum AI. Transmitting Pain and Itch Messages: A Contemporary View of the Spinal Cord Circuits that Generate Gate Control. *Neuron.* 2014;82(3):522-536. doi:10.1016/j.neuron.2014.01.018
68. Fuller AM, Luiz A, Tian N, et al. Gate control of sensory neurotransmission in peripheral ganglia by proprioceptive sensory neurons. *Brain.* 2023;146(10):4033-4039. doi:10.1093/brain/awad182
69. Petersen-Zeitl KR, Basbaum AI. Second messengers, the substantia gelatinosa and injury-induced persistent pain. *Pain.* 1999;82(SUPPL.1). doi:10.1016/S0304-3959(99)00132-3
70. Shanley KJ. Pathophysiology of pruritus. *Vet Clin North Am Small Anim Pract.* 1988;18(5):971-981. doi:10.1016/S0195-5616(88)50101-8
71. Ropero Peláez FJ, Taniguchi S. The gate theory of pain revisited: Modeling different pain conditions with a parsimonious neurocomputational model. *Neural Plast.* 2016;2016. doi:10.1155/2016/4131395
72. Pereira PJS, Lerner EA. Gate Control Theory Springs a Leak. *Neuron.* 2017;93(4):723-724. doi:10.1016/j.neuron.2017.02.016
73. Moayed M, Davis KD. Theories of pain: From specificity to gate control. *J Neurophysiol.* 2013;109(1):5-12. doi:10.1152/jn.00457.2012
74. Ossipov MH, Dussor GO, Porreca F. Central modulation of pain. *J Clin Invest.* 2010;120(11):3779-3787. doi:10.1172/JCI43766.reduced
75. De Felice M, Ossipov MH. Cortical and subcortical modulation of pain. *Pain Manag.* 2016;6(2):111-120. doi:10.2217/pmt.15.63
76. Medoff ZM, Colloca L. Placebo analgesia: understanding the mechanisms. *Pain Manag.* 2016;5(2):89-96. doi:10.2217/pmt.15.3.Placebo
77. Chen C, Niehaus JK, Dinc F, et al. Neural circuit basis of placebo pain relief. *Nature.* 2024;632:1092-1125. doi:10.1038/s41586-024-07816-z
78. Pagliusi M, Gomes F V. The Role of The Rostral Ventromedial Medulla in Stress Responses. *Brain Sci.* 2023;13(5):1-10. doi:10.3390/brainsci13050776
79. Benarroch EE. Descending monoaminergic pain modulation: Bidirectional control and clinical relevance. *Neurology.* 2008;71(3):217-221. doi:10.1212/01.wnl.0000318225.51122.63
80. Lockwood S, Dickenson AH. What goes up must come down: insights from studies on descending controls acting on spinal pain processing. *J Neural Transm.* 2020;127(4):541-549. doi:10.1007/s00702-019-02077-x
81. Colloca L, Klinger R, Flor H, Bingel U. Placebo analgesia: Psychological and neurobiological mechanisms. *Pain.* 2013;154(4):511-514. doi:10.1016/j.pain.2013.02.002
82. Neyama H, Wu Y, Nakaya Y, et al. Opioidergic activation of the descending pain inhibitory system underlies placebo analgesia. *Sci Adv.* 2025;11(3):1-16. doi:10.1126/sciadv.adp8494
83. Fenton BWF, Shih E, Zolton J. The neurobiology of pain perception in normal and persistent pain Bradford W Fenton, Elim Shih and Jessica Zolton. *Pain Manag.* 2015;4(July 2015):1-26.
84. Gallace A, Bellan V. The Parietal Cortex and Pain Perception: A Body Protection System. Vol 151. 1st ed. Elsevier B.V.; 2018. doi:10.1016/B978-0-444-63622-5.00005-X
85. Benarroch EE. Involvement of the nucleus accumbens and dopamine system in chronic pain. *Neurology.* 2016;87(16):1720-1726. doi:10.1212/WNL.0000000000003243

86. Guénette SA, Giroux MC, Vachon P. Pain perception and anaesthesia in research frogs. *Exp Anim*. 2013;62(2):87-92. doi:10.1538/expanim.62.87
87. Meng J, Li X, Peng W, Li Z, Shen L. The interaction between pain and attractiveness perception in others. *Sci Rep*. 2020;10(1):1-11. doi:10.1038/s41598-020-62478-x
88. Taesler P, Rose M. Multivariate prediction of pain perception based on pre-stimulus activity. *Sci Rep*. 2022;12(1):1-9. doi:10.1038/s41598-022-07208-1
89. Müller R, Segerer W, Ronca E, et al. Inducing positive emotions to reduce chronic pain: a randomized controlled trial of positive psychology exercises. *Disabil Rehabil*. 2022;44(12):2691-2704. doi:10.1080/09638288.2020.1850888
90. Kaur A, Guan Y. Phantom limb pain: A literature review. *Chinese J Traumatol - English Ed*. 2018;21(6):366-368. doi:10.1016/j.cjtee.2018.04.006
91. Flor H. Phantom-limb pain: characteristics, causes, and treatment. *Lancet*. 2002;1(July):182-189.
92. Urits I, Seifert D, Seats A, et al. Treatment Strategies and Effective Management of Phantom Limb–Associated Pain. *Curr Pain Headache Rep*. 2019;23(9):1-7. doi:10.1007/s11916-019-0802-0
93. Kato F, Sugimura YK, Takahashi Y. Pain-associated neural plasticity in the parabrachial to central amygdala circuit: Pain changes the brain, and the brain changes the pain. *Adv Exp Med Biol*. 2018;1099:157-166. doi:10.1007/978-981-13-1756-9_14
94. Afridi B, Khan H, Akkol EK, Aschner M. Pain Perception and Management. *J Curr Mol Pharmacol*. 2021;14(5):678-688. doi:10.2174/1874467213666200611142438.Pain
95. Wu H, Saini C, Medina R, Hsieh SL, Meshkati A, Sung K. Pain without presence: a narrative review of the pathophysiological landscape of phantom limb pain. *Front Pain Res*. 2025;(February):1-10. doi:10.3389/fpain.2025.1419762
96. Melzack R. From the gate to the neuromatrix. *Pain*. 1999;6(1):121-126.
97. Trout KK. The Neuromatrix Theory of Pain : Implications for Selected Nonpharmacologic Methods of Pain Relief for Labor. *J Midwifery Womens Heal*. 2004;49(6):482-488. doi:10.1016/j.jmwh.2004.07.009
98. Copits BA, Pullen MY, W. GIR. Spotlight on pain: optogenetic approaches for interrogating somatosensory circuits. *Pain*. 2017;157(11):2424-2433. doi:10.1097/j.pain.0000000000000620.Spotlight
99. Deisseroth K. Optogenetics : 10 years of microbial opsins in neuroscience. *Nat Neurosci*. 2015;18(9):1213-1225.
100. Baier H, Scott EK. Genetic and Optical Targeting of Neural Circuits and Behavior – Zebrafish in the Spotlight. *Curr Opin Neurobiol*. 2010;19(5):553-560. doi:10.1016/j.conb.2009.08.001.Genetic
101. Wang Y, Hu Z, Ju P, et al. Viral vectors as a novel tool for clinical and neuropsychiatric research applications. *Gen Psychiatry*. 2018;(31):1-9. doi:10.1136/gpsych-2018-000015
102. Zhang C, Hong Z, Li H, et al. Optogenetic activation of mechanical nociceptions to enhance implant osseointegration. *Nat Commun*. 2025;16:1-21. doi:10.1038/s41467-025-58336-x
103. Montgomery KL, Iyer SM, Christensen AJ, Deisseroth K, Delp SL. Beyond the brain : Optogenetic control in the spinal cord and peripheral nervous system. *Science (80-)*. 2016;8(337):1-13.
104. Shen Y, Campbell RE, Cote DC, Paquet ME. Challenges for Therapeutic Applications of Opsin-Based Optogenetic Tools in Humans. *Front Neural Circuits*. 2020;14(July):1-11. doi:10.3389/fncir.2020.00041