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Review article

UNDERSTANDING NEUROBIOLOGICAL PATHWAYS OF PAIN REGULATION AND NOVEL THERAPEUTICS FOR PAIN MANAGEMENT

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Abstract

Background: *Pain, as unpleasant as it may appear, is a highly vital defense mechanism. It alerts the body to potential or actual injuries or diseases so that pre-emptive measures can be taken. Noxious stimuli transmit impulses to the spinal cord, which conveys the information to the brain. When nociception fibers detect noxious stimuli on the skin or in interior organs, pain develops. The detection of the signal is taken up by the dorsal horn of the spinal cord and brain stem, which transfers it to various parts of the brain. This route is facilitated by unique substances known as neurotransmitters.* ***Objective:*** *The objective of this review is to understand the role of numerous endogenous neurotransmitters and the regulation of pain processing pathways.* ***Methods:*** *All data were identified, retrieved, and evaluated by searching for peer-reviewed journal articles using Google Scholar and PubMed.* ***Discussion:*** *Neurotransmitters are endogenous chemical messengers, which carry signals from one neuron to another "target" neuron, muscle cell, or glandular cell across a chemical synapse. Some neurotransmitters are excitatory, facilitating message transmission, whereas others are inhibitory, inhibiting transmission. These neurotransmitters play a crucial role in pain regulation and a deeper understanding of the neurobiological pathways could open a doorway for the development of novel therapeutics for pain.* ***Conclusion:*** *As a whole, the current review focused on the cellular and molecular processes that support the pain pathway. Furthermore, the pivotal classes of neurotransmitters involved in pain mechanism viz transduction, transmission, and regulation, as well as their locus and potential pharmacological effects, have been thoroughly explored.*

Keywords: Pain, noxious stimuli, neurotransmitters, cellular mechanism.

Introduction

Pain is an essential but unpleasant sensation caused by cellular damage or injury. The processes by which noxious stimuli cause animals to feel pain are intricate. Noxious impulses are transduced at the periphery and conveyed to the CNS, where they undergo significant modulation. Finally, the data is sent to the brain, where it is

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translated into pain [1]. Plasticity can also occur in the pain pathway, and hyperalgesia and allodynia can arise as a result of peripheral and central sensitization. Addressing the adaptability of pain and analgesia in various pain states may help to enhance treatments for the two most common forms of pain, neuropathic and inflammatory pain in which, damage to nerves and tissues causes changes at both the peripheral and central levels [2]. Drugs that act on specific sodium channels in the peripheral nerve may solely target pain-related activity. Peripheral nerve activity may be controlled by agents that act on the peripheral mediators of pain. Cyclo-oxygenase 2 inhibitors, a novel class of non-steroidal anti-inflammatory medicines with no gastrointestinal effects, are becoming accessible. The release of peptides and glutamate in the spinal cord activates several receptors, including the glutamate N-methyl-D-aspartate receptor, which works in tandem with the glutamate N-methyl-D-aspartate receptor. Spinal hypersensitivity is caused by other spinal systems. One strategy is to prevent excitability from being generated, although analgesia may be produced by increasing inhibitions. Opioids work by inhibiting central and peripheral C fiber terminals, spinal neurons, and supraspinal processes via presynaptic and postsynaptic inhibitory effects [3]. However, our understanding of pain mechanisms in the brain is relatively limited. Molecular biology and animal models of clinical pain have identified other potential targets, but the idea of a "silver pill" is unlikely. Pain perception involves a huge number of ion channels, receptors, and cell types, and it is hoped that a greater knowledge of them may lead to novel and improved pain treatments.

The basic mechanism of pain

With the presence of noxious stimuli, the basic mechanism of pain follows three episodes *viz* transduction, transmission, and modulation.

i. Transduction: Following events occur in the transduction process: At first, the stimulus-induced events are transformed into chemical tissue events. Chemical tissue events, as well as synaptic cleft events, are then translated to electrical events within the neurons. Furthermore, synapses convert electrical impulses in neurons to chemical events [4].
ii. Transmission: Transmission occurs once transduction is accomplished by communicating the electrical signals inside the neural circuits. However, neurotransmitters present in the synaptic gap are used to convey transmit information from a postsynaptic endpoint of one cell to a presynaptic endpoint of another cell [4].
iii. Modulation: By up or down-regulation, modulation occurs at all stages of nociceptive pathways *via* the dorsal horn, primary afferent neuron, and higher brain center. All the above-mentioned events lead to the initiation of pain,

which allows us to feel the pain sensation triggered by the stimulus [4]. The basic mechanism of pain is depicted in Fig 1.

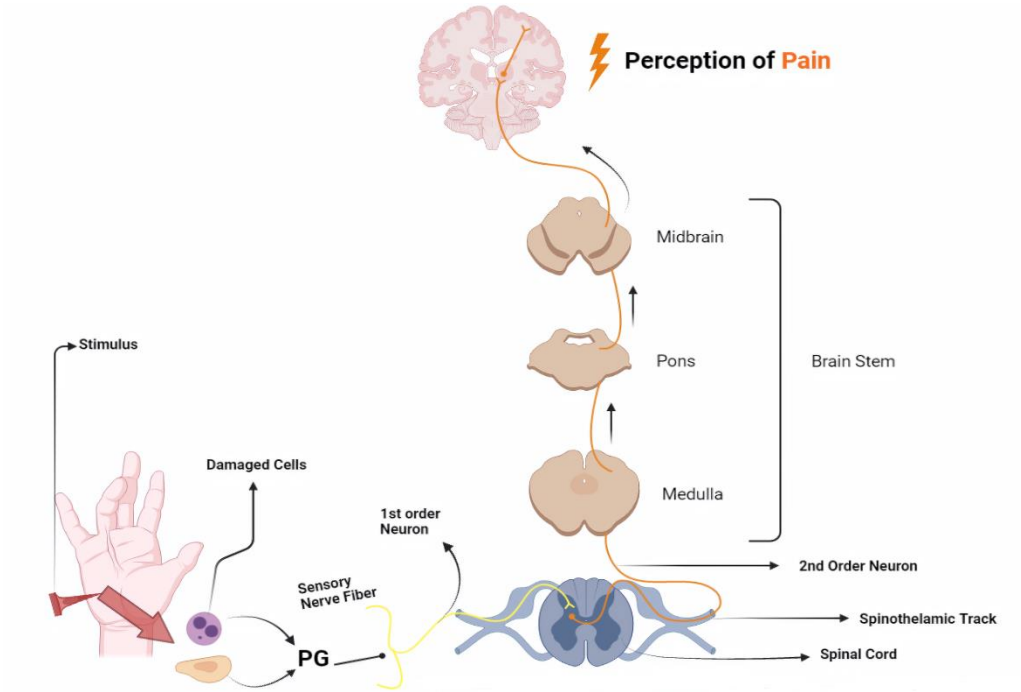

Fig. 1: Depiction of the basic mechanism of pain (Figure created with BioRender.com).

Types of Pain

Based on the mechanisms, symptoms, and syndromes, pain is divided into three categories *viz* inflammatory pain, nociceptive pain, and neuropathic pain.

Inflammatory pain

Inflammation classically describes four key signs. Each of which has a *Latin* derivation. Color or heat, dolor or pain, rubor or redness, and tumor or swelling. Sometimes these four signs combined to cause the fifth sign, which is "function-laesa" or temporary loss of function due to pain or swelling. Inflammation is caused by different types of insults like infections by pathogens, injuries, and exposure to toxins. The ultimate goal of inflammation is to respond to stimuli, protect from harmful agents and restore balance [5]. Oftentimes, that includes eliminating the cause of tissue injury, cleaning out necrotic and dead cells, and starting tissue repair. In this process, inflammation involves activation and sensitization of primary afferent neurons leading to pain sensation. Inflammation can cause three different types of pain responses- allodynia, hyperalgesia, and sympathetic maintained pain.

The localized inflammatory response induces the release of arachidonic acid, which is converted to inflammatory prostaglandins *via* the cyclooxygenase pathway ultimately leading to pain [5]. Furthermore, inflammation-related pain can be divided into two categories- acute and chronic pain. Inflammatory acute pain is usually severe and lasts only a few minutes, and it is caused by damaging stimuli that are ordinarily transmitted by the Aδ-fibers. Prolonged inflammation, often known as inflammatory chronic pain, lasts longer than expected and is often mediated by C-fibers [6].

Nociceptive pain

Nociceptive pain refers to pain due to an actual or potentially tissue-damaging injury that is transduced and transmitted *via* nociceptors. The response of our bodies' sensory nerve systems to actual or potentially damaging stimuli is known as nociception or nociperception. Nociceptors are sensory endings that are stimulated by noxious stimuli and are involved in the first phase of the pain perception mechanism [7]. The C-fibers and Aδ are two different types of primary afferent nociceptors that respond to unpleasant stimuli in our body. Both these two nociceptors are widely located in muscle, skin, bones, joint capsule, and other internal organs as well. They detect potentially damaging mechanical, chemical, and thermal stimuli [7].

Neuropathic pain

The peripheral nervous system communicates with the rest of the body by connecting nerves in the brain and spinal cord. Signals from the brain could reach the arms, legs, and other internal organs in this way. Neuropathic pain, commonly known as neuropathy or nerve pain, is caused when nerves are injured or destroyed. It causes fatigue, numbness, and moderate to severe pain. Allodynia is frequently accompanied by neuropathy[8]. Allodynia is a type of central pain sensitization caused by repetitive non-painful receptor stimulation. It causes a pain sensation in response to stimuli that are normally non-painful. Diabetes is a common cause of neuropathy, but it can also be caused by injuries, infections, or exposure to specific toxins. Nociceptors exhibit a dynamic expression of ion channels such as voltage-gated sodium channels during neuropathic pain conditions. In addition, voltage-gated sodium channels are important regulators of initiation and propagation of action potentials as well as neuronal excitability [8].

Role of neurotransmitter in sensitization of pain

The pain perception is mediated by a variety of neurotransmitters including tachykinins, adenosine triphosphate, adenosine, histamine, serotonin, glutamate, leukotriene B_4, prostaglandin E_2, prostaglandin I_2, bradykinin, nerve growth factor, proton, nitric oxide, norepinephrine, ϒ-aminobutyric acid, calcitonin gene-related

peptide, glycine, and cannabinoids which are summarized in Table 1 along with their expression, receptor mechanism, and pharmacological mechanism.

Tachykinins

Tachykinins are categorized under the neuropeptides family. With its three members family *viz* neurokinin A, neurokinin B, and substance P produced from peripheral terminals of the sensory nerve fibers like skin and muscle can induce neurogenic inflammation through proteolytic cleavage of pre-protachykinins. The neurokinin A, neurokinin B, and substance P bind to their corresponding receptors preferentially based on their affinity. Based on their affinity, neurokinin A binds with neurokinin type 2 receptor, neurokinin B binds to neurokinin type 3 receptor, and substance P binds with neurokinin type 1 receptor respectively. All of the receptors described above are Gq-Protein-coupled receptors, which mediates through phospholipase C/inositol triphosphate and diacylglycerol/protein kinase C signaling pathways upon activation, thereby showing excitatory effects [9].

Adenosine Triphosphate

Adenosine triphosphate is a key intracellular messenger that is liberated locally by the injured tissues and activates its receptors directly. For binding to its receptor, adenosine triphosphate is converted to adenosine through the presence of ectonucleotidases which binds to its receptor *i.e* ionotropic purino receptor. The ionotropic purino receptor that is of six types shows its action in the region of sensory neurons. The most selectively shown ionotropic purino receptor type 3 receptors are widely expressed in the region of a small C-fibered nociceptor. After, adenosine triphosphate attaches itself to the ionotropic purino receptor type 3 receptors Na^+ ion crosses the channel and because of this membrane depolarizing occurs. Due to this, various Ca^+ sensitive intracellular processes and as a result both pain and hyperalgesia could be perceived. Adenosine triphosphate can promote glutamate release by acting on nociceptors presynaptically. Furthermore, adenosine a by-product of adenosine triphosphate metabolism binds to either adenosine type 1 receptor or adenosine type 2 receptor. Type 1 adenosine receptor is G_i-protein coupled receptors for inhibitory effects and type 2 adenosine receptor are G_s-protein coupled receptors which are located both centrally and peripherally sensitize the nociceptor through the cyclic adenosine monophosphate/phosphokinase A pathways [10, 11].

Cytokines

The platelet-activating factor is triggered to release serotonin or 5-HT from circulating platelets during the inflammation-induced mast cell degranulation process. The 5-HT receptors are all G-protein coupled receptors, except for the 5-hydroxytryptamine type 3 receptor, which is a ligand-gated ion channel. The 5-

hydroxytryptamine type 2A receptor and the 5-HT3 receptor are the two principal subtypes of 5-HT receptors found on sensory neuron terminals. Among them, the 5-hydroxytryptamine type 2A receptor is Gq-protein-coupled, which raises the pain sensation *via* regulating phospholipase C/ inositol triphosphate and diacylglycerol/protein kinase C pathways, while stimulation of $5HT_3$ receptor causes excitatory effects. Furthermore other cytokines, including TNF-α and IL-1β, also play an important role in causing hyperalgesia by having a significant pro-inflammatory impact, as well as interacting synergistically with a nerve growth factor [12].

Glutamate

The amplest excitatory neurotransmitter in the vertebrate system, manifesting itself at peripheral sites of inflammation and contributing to more than 50% of brain synapses. It regulates nociception and the release of neurotransmitters from terminal afferents neurons. In general, sensory neurons exhibit a sufficient number of glutamate receptors, including N-methyl-D-aspartate receptors and alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptors [13].

Leukotriene B_4

Leukotriene B_4 is considered an eicosanoid inflammatory mediator formed within the leukocytes by the oxidation of arachidonic acid. After an injury, the arachidonic acid breaks into 5-hydroperoxy eicosatetraenoic acid by the action of enzyme lipooxygenase and thereafter hydrolyzed into leukotriene B_4 by leukotriene A_4 hydrolase. Leukotriene B_4 can elicit hyperalgesia indirectly in the presence of polymorphonuclear leucocytes, most likely *via* the afferent terminal route. By raising the cyclic adenosine monophosphate/phosphokinase A activities, Leukotriene B_4 can induce nociceptors to become more peripherally sensitive [14, 15].

Prostaglandins

Prostaglandins are synthesized from arachidonic acid *via* the action of the enzyme cyclooxygenase. The two main prostaglandins are PGE_2 and PGI_2. PGE_2 receptors are classified into 4 types *viz* prostaglandin E_2 receptor type 1-4 ($EP_{1\text{-}4}$), while the receptor of PGI_2 is called prostacyclin receptor (IP). EP_1 is a Gq-protein-coupled receptor that follows phospholipase C/inositol triphosphate and diacylglycerol/protein kinase C signaling pathways. $EP_{2,4}$ and IP are G_s-protein-coupled receptors and follow the cyclic adenosine monophosphate/protein kinase A/adenylyl cyclase signaling pathway, whereas EP_3 is G_i-protein-coupled receptor produces inhibitory effects. Besides this, prostaglandin promotes the action of other chemical mediators like bradykinin and serotonin, along with calcitonin gene-related peptide and Substance P to be released. Furthermore, a rise in bradykinin

triggers the secretion of prostaglandins and thus produces a “self-sensitizing effect” [16].

Bradykinin

Bradykinin is a protein belonging to the kinin family. Bradykinin is considered an inflammatory mediator is produced locally at the site of inflammation through the fragmentation of large molecules called kininogens. Bradykinin receptor type B_1 or bradykinin receptor type B_2 is Gq- a protein-coupled receptor that binds to bradykinin causing peripheral sensitization in the nociceptive afferent nerve fibers. The activation of bradykinin receptor type B_1 or bradykinin receptor type B_2 leads to activation of phospholipase C to break down the phosphatidylinositol 4,5-bisphosphate into inositol triphosphate and diacylglycerol, further diacylglycerol switch on the protein kinase C, showing a rise in Ca^{2+} conductance. Moreover, bradykinin can also act synergistically with other substances like nerve growth factor and prostaglandins which further stimulate the formation of pro-inflammatory cytokines [17, 18].

Nerve Growth Factor

The mediator for chronic pain, locally discharge at the site of abrasion by fibroblast is a neurotrophic factor of neuropeptide known as a nerve growth factor. It can stimulate a rapid onset of thermal and mechanical hyperalgesia by expressing nerve growth factors swiftly after the inflammatory abscess is produced. Tropomyosin receptor kinase which is a nerve growth factor-dependent nerve fiber has a high tendency for nerve growth factor receptors. Nerve growth factor receptor is abundantly expressed in primary afferent neurons, suggesting that it plays a significant role in peripheral sensitization activation. Nerve growth factor, for example, can promote mast cell degranulation and the synthesis of histamine and serotonin, as well as induce the release of additional nerve growth factor, so amplifying inflammatory signals [19].

Proton

An injured site is generally more acidic than homeostasis thus the protons are more in numbered at the injured site. Around the injured site, a rising number of these protons activates both the vanilloid receptor 1 and acid-sensing ion channels. Moreover, studies have shown that exposing primary afferent nerve fibers to a pH less than 6 can trigger the acid-sensing ion channels [20]. In presence of capsaicin or heat stimuli, this proton can also stimulate vanilloid receptor 1when pH is less than 5.5 [20]. When both vanilloid receptor 1 and acid-sensing ion channels are activated, the expression of histamine, bradykinin, and prostaglandin E_2 at the injury site further raises the intracellular Ca^{2+} influx, thus improves the expression of sensory neuron-specific Na^{+} channels and vanilloid receptor 1 [21]. As a result of

the influx of Na^+, an action potential is a spawn, leading the afferent neurons to become sensitized. The release of calcitonin gene-related peptide and substance P is triggered by an increase in intracellular Ca^{2+}, whereas it can also desensitize vanilloid receptor 1 [22].

Norepinephrine

The primary neurotransmitter of the adrenergic systems, norepinephrine, is produced in nerve terminals from phenylalanine, an essential α-amino acid. An enzyme, tyrosine hydroxylase turns phenylalanine into tyrosine, which is then transformed into 3,4-dihydroxyphenylalanine. 3,4-dihydroxyphenylalanine is subsequently transformed into dopamine, which is the main precursor of norepinephrine that is stored in nerve terminal vesicles. Norepinephrine contains receptors like α_1-$G_q\alpha$, α_2-$G_i\alpha$, β-$G_s\alpha$ protein-coupled receptors. Among them, α_1-$G_q\alpha$ and β-$G_s\alpha$ are mostly located in postsynaptic neurons, whereas α_2-$G_i\alpha$ are located in presynaptic neurons. As a result, activation of the α_2-$G_i\alpha$ protein-coupled receptors reduces norepinephrine release out of the synapse by blocking Ca^{2+} influx. Besides this, the attachment of norepinephrine with α_1-$G_q\alpha$ and β-$G_s\alpha$ protein-coupled receptors which are present in postsynaptic nerves provoke the phospholipase C/phosphokinase C and cyclic adenosine monophosphate/phosphokinase A signaling pathways, consequently and causes stimulatory effects [23].

ϒ-Aminobutyric Acid

ϒ-Aminobutyric Acid which is considered the most diverse inhibitory neurotransmitter in the mammalian central nervous system contributes nearly 40% of our brain synapses and is present inside the neurons of the cerebellum, spinal cord, and neocortex [24]. ϒ-Aminobutyric Acid can interact with ionotropic $GABA_A$-receptors or metabotropic $GABA_B$-receptors in the nervous system, which are both extensively distributed in the central nervous system, as well as concentrated at presynaptic nerve terminals also. When ϒ-Aminobutyric Acid binds to the $GABA_A$ receptor, the inflow of extracellular Cl^- into the neurons takes place thereby reducing membrane potential thus producing an inhibitory effect. Moreover, ϒ-Aminobutyric acid-binding to $GABA_B$ receptors, inhibits cyclic adenosine monophosphate production, since the $GABA_B$ receptor is a G_i-protein-coupled receptor [25].

Calcitonin Gene-Related Peptide

Calcitonin Gene-Related Peptide is synthesized in both the peripheral and nervous systems, however, it is found largely in the primary afferent nerves. Calcitonin Gene-Related Peptide mimics the excitatory effects of substance P, produces the release of Ca^{2+} ions, and is associated with the transmission of noxious stimulation

[26]. The receptors present in Calcitonin Gene-Related Peptide are Gs-protein-coupled which indicates Calcitonin Gene-Related Peptide-mediated pain transmission [27].

Cannabinoids

The cannabinoid is a type of neurotransmitters that attaches themselves to their receptors and regulates the release of neurotransmitters in the brain. Cannabinoids attach to G_i-protein coupled cannabinoid type 1 receptors which are abundantly expressed in the presynaptic and postsynaptic region of the brain and spinal cord, along with G_i-protein-coupled cannabinoid type 2 receptors, which are mostly found in the immune system [28]. The expression of cannabinoid type 1 receptor and cannabinoid type 2 receptors suppressed the formation of intracellular cyclic adenosine monophosphate, thus produces a tremendous reduction of the stimulatory effect within the neurons. Furthermore, cannabinoid type 2 receptor activation can inhibit degranulation of mast cells and the production of pro-inflammatory mediators, making a decrease in pain sensation drastically and effectively [29].

Opioid Peptides

Binding of opioid receptors *viz* δ-opioid receptors, κ-opioid receptors, and μ-opioid receptors with the peptides are collectively called opioid peptides. All opioid receptors are classified under G_i-protein-coupled receptor, which implies that when they are activated, they suppress cyclic adenosine monophosphate/adenylyl cyclase activity. The opioid receptors are predominantly found in both the regions of postsynaptic neurons dendrites and primary afferent neurons, and there are two opioid peptides *viz* dynorphin and enkephalin produced endogenously into the interneurons of the dorsal horn. Such peptides block the transmission of excitatory neurotransmitters from the afferent nerve terminals, thereby attenuating the excitability of neurons and overall controls the pain sensation [30].

Table 1: Neurotransmitters along with their expression and pharmacological mechanism

Neurotransmitters	Expression of neurotransmitters	Receptors: Mechanism	Inhibitory/ Excitatory effects	Pharmacological mechanism	References
Inflammatory mediators					
Tachykinins-Neurokinin A, neurokinin	Peripheral nervous system (particularly in C-fibers) and	Neurokinin type 1 receptor, Neurokinin	Excitatory	Mediates neurogenic inflammation; activation of nitric oxide synthase and arachidonic acid	[9, 31]

B, and substance P (Neuropeptides)	Central nervous system (predominantly in the dorsal horn of the spinal cord)	type 2 receptor, and Neurokinin type 3 receptor: Phospholipase C/Inositol triphosphate, Diacylglycerol/Protein kinase C		pathways for the release of nitric oxide and prostaglandin E2 respectively; improve Cyclic adenosine monophosphate/protein kinase A activities	
Adenosine triphosphate and adenosine (Purine)	Peripheral nervous system and Central nervous system	Purino receptor-Na^+/K^+; A_1 and A_2-Adenylyl cyclase/Cyclic adenosine monophosphate/Protein kinase A	Excitatory (Purino receptor and A_2)/ Inhibitory (A_1)	Improve glutamate release; sensitize the nociceptors	[10, 32]
Histamine (Monoamine)	Peripheral nervous system and Central nervous system	$Histamine_1$-Phospholipase C/Inositol triphosphate, Diacylglycerol/Protein kinase C	Excitatory	Exert synergistic interaction with nerve growth factor	[33, 34]
Serotonin	Peripheral nervous system	5-hydroxytry	Excitatory	Exert synergistic interaction with nerve	[35, 36]

	and Central nervous system	ptamine type 2A receptor-Phospholipase C/Inositol triphosphate, Diacylglycerol/Protein kinase C; 5-hydroxytryptamine type 3 receptor-Na^+/K^+		growth factor	
Glutamate (amino acid)	Peripheral nervous system (particularly in C-fibres) and Central nervous system	N-methyl-D-aspartate receptors and Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor-$Mg^{2+}/Ca^{2+}/Na^+/K^+$	Excitatory	----	[37]
Leukotriene B_4	Peripheral nervous system	Leukotriene B_4 type 1 receptor and Leukotriene B_4 type 1 receptor 2-	Excitatory/ Inhibitory	Promote cytokine production; sensitize nociceptors; recruit neutrophils to injury site	[38]

		Adenylyl cyclase/Cyclic adenosine monophosphate/Protein kinase A or Phospholipase C			
Prostaglandin E_2 and Prostaglandin I_2	Peripheral nervous system and Central nervous system	Prostaglandin E2 receptor type 1-Phospholipase C/Inositol triphosphate, Diacylglycerol/Protein kinase C; Prostaglandin E2 receptor type 2, Prostaglandin E2 receptor type 3, Prostaglandin E2 receptor type 4, and Prostacyclin receptor-Adenylyl cyclase/Cy	Excitatory (Prostacyclin receptor, Prostaglandin E2 receptor type 1, Prostaglandin E2 receptor type 2, and Prostaglandin E2 receptor type 4e); Inhibitory (Prostaglandin E2 receptor type 3)	Augment the release of bradykinin, calcitonin gene-related peptide, histamine, interleukin-2, serotonin, and substance P	[39, 40]

		clic adenosine monophosphate/Protein kinase A			
Bradykinin (Neuropeptide)	Peripheral nervous system and Central nervous system (hypothalamus and pituitary)	Bradykinin receptor type B1 and Bradykinin receptor type B2-Phospholipase C/Inositol triphosphate, Diacylglycerol/Protein kinase C	Excitatory (Bradykinin receptor type B1 and Bradykinin receptor type B2)	Exert synergistic interaction with nerve growth factor and prostaglandin; augment the release of prostaglandin, nerve growth factor, and proinflammatory cytokines *i.e* Interleukin2	[41]
Nerve growth factor (Neuropeptide)	Peripheral nervous system and Central nervous system	Tropomyosin receptor kinase A-Phosphoinositide 3-kinase	Excitatory	Augment the release of serotonin, histamine; cause the mast cells degranulation	[42]
Proton	Peripheral nervous system and Central nervous system	Acid-sensing ion channels and Vanilloid receptor 1-Na^+/K^+	Excitatory	Improve the release of bradykinin, substance P, calcitonin gene-related peptide, histamine, and prostaglandin E2	[43, 44]
Nitric oxide (Gasotransmi	Peripheral nervous system	Soluble guanylyl	Excitatory/ Inhibitory	Recruited to the site of inflamed tissue	[45]

tter)	and Central nervous system	cyclase/ Cyclic guanosine monophosphate			
Norepinephrine (Monoamine)	Peripheral nervous system and Central nervous system	α1- Phospholipase C/inositol triphosphate, Diacylglycerol/Protein kinase C α2- Adenylyl cyclase/Cyclic adenosine monophosphate/Protein kinase A	Excitatory (α1 and β)/ Inhibitory (α2)	---	[23]
Non-inflammatory mediators					
ϒ-aminobutyric acid (Amino acid)	Peripheral nervous system and Central nervous system	ϒ-aminobutyric acid type A receptor-Cl^-/K^+ (Inhibitory postsynaptic potentials); ϒ-aminobutyric acid type B receptor-Adenylyl cyclase/Cy	Inhibitory (ϒ-aminobutyric acid type A receptor and ϒ-aminobutyric acid type B receptor)	---	[46]

		clic adenosine monophosphate/Protein kinase A			
Calcitonin gene-related peptide (Amino acid)	Peripheral nervous system and Central nervous system (predominantly in the dorsal horn of spinal cord)	Calcitonin receptor-like receptor-Adenylyl cyclase/Cyclic adenosine monophosphate/Protein kinase A	Excitatory	Synergistic with the excitatory effect of substance P	[47, 48]
Glycine (Amino acid)	Central nervous system	Glycine receptor-Cl^- (Inhibitory postsynaptic potentials)	Inhibitory	---	[49]
Cannabinoids (Lipid)	Peripheral nervous system and Central nervous system (brain)	Cannabinoid type 1 receptor and cannabinoid type 2 receptors-Adenylyl cyclase/Cyclic adenosine monophosphate/Protei	Inhibitory (Cannabinoid type 1 receptors and cannabinoid type 2 receptors)	Release of pro-inflammatory mediators and prevent the mast cells degranulation	[50, 51]

		n kinase A			
Opioid peptides (Neuropeptide)	Peripheral nervous system and Central nervous system (hippocampus, hypothalamus, spinal cord, and striatum)	δ-opioid receptors, κ-opioid receptors, and μ-opioid receptors-Adenylyl cyclase/Cyclic adenosine monophosphate/Protein kinase A	Inhibitory	---	[52]

Novel therapeutic platform for the management of pain relief

By establishing new molecular targets and novel ways to treat pain, we may indeed be able to develop novel medications to effectively treat acute and chronic inflammatory pain without the downsides of present opioid medications. Table 2 and Table 3 illustrated the pain related target along with their mechanism of action, and venom derived peptide used in pain therapy.

Table 2: Molecular target, activators/inhibitors, mechanism of action, and concluding remarks

Molecular target	Activators/Inhibitors	Mechanism of action	Concluding remarks	References
Opioid receptor-like receptor 1/Nociceptin receptor	Activators- Cebranopadol, MCOPPB, and NNC63-0532; Inhibitors- JTC-801, LY-2940094, and SB 61211.	Supraspinal stimulation has a pronociceptive effect, while spinal and peripheral stimulation has an anti-nociceptive effect.	Completed phase I trial and continuing phase II and III clinical trials, but no findings have been published.	[53]

Kappa opioid receptor	Activators- CR 665, CR 845; Inhibitors- Buprenorphine.	Anti-nociceptive activity is primarily peripheral; opioid-induced hyperalgesia is linked to spinal activation.	In clinical studies for postoperative pain, peripherally limited agonists lower opioid intake and pain ratings; the antagonism is related to an anti-hyperalgesic response in human pain models.	[54, 55]
Opioid heteromers	Activators- N-naphthoyl-β-naltrexamine; Inhibitors- CYM51010.	Cannabinoid receptor type 1 and mu-opioid receptor heteromers are colocalized in the rostral ventromedial medulla and dorsal root ganglion; mu-opioid receptor heteromer found in dorsal root ganglion and rostral ventromedial medulla.	Initial phases of development.	[56]
Serotonin, norepinephrine, and dopamine	Activators- Antidepressant; Inhibitors- Duloxetine, milnacipran, and venlafaxine.	Inhibit descending pathway.	Serotonin and norepinephrine reuptake inhibitors and tricyclic antidepressants have strong evidence of efficacy in	[57, 58]

			peripheral neuropathic pain disorders; serotonin and norepinephrine reuptake inhibitors have evidence of efficacy in nociceptive pain; Serotonin and norepinephrine reuptake inhibitors have minimal evidence of efficacy.	
Alpha 2 receptor	Activators- Clonidine, tizanidine, and dexmedetomidine.	Pre- and postsynaptic pain processing are suppressed by anti-nociceptive activity in the spinal region.	Administration *via* intrathecal route may be helpful in mixed or neuropathic pain conditions; clinical evidence suggests modest long-term pain reduction.	[59]
Histamine receptor	Activators- Immepip; Inhibitors- GSK 189254, thioperamide.	Histamine release is inhibited by receptor H3 activation; Substance P and Calcitonin gene-related peptide release is reduced by peripheral H3 receptor activation;	Preclinical data for analgesia in H3 receptor-activated nociceptive pain models; preclinical data in neuropathic pain models with brain-penetrating H3 receptor antagonists.	[60]

		nociceptive transmission is reduced by intracerebral histamine signaling.		
Cannabinoid receptors	Activators- AM 1241.	Cannabinoid receptors type 1 on the presynaptic membrane impaired neurotransmitter release while Cannabinoid receptors type 2 receptors are activated in neuropathic pain models.	Cannabinoids have strong evidence for treating neuropathic pain and limited evidence for treating nociceptive pain, but they have a high rate of side effects; preclinical evidence of cannabinoid receptors type 1 receptor agonists in neuropathic and nociceptive pain models, but negative findings in clinical studies; preclinical evidence of cannabinoid receptors type 2 receptor agonists in neuropathic and nociceptive pain models, but no clinical data.	[61]
Voltage-gated	Activators- Ca^{2+};	In the central and	N-type channel	[62]

calcium channels	Inhibitors- Mibefradil, gabapentin, ethosuximide, and Z944	peripheral neurological systems, voltage-gated calcium channels regulate neurotransmitter release, ion conductance, and neuronal excitability.	blocking agent has preclinical efficacy in neuropathic pain, but clinical data are lacking; T-type channel blocking agent has preclinical efficacy in neuropathic and nociceptive pain models; clinical trials are still going on, but no findings have been released yet.	
Voltage-gated sodium channels	Activators- Na^+, brevetoxin B, and ciguatoxin; Inhibitors- TV-45070, CNV1014802, and PF-05089771.	In neurons, it is in charge of the initiation and propagation of action potentials.	Voltage-gated sodium channels 1.7 inhibition has been shown in preclinical studies to alleviate neuropathic and nociceptive pain; Preclinical evidence for voltage-gated sodium channels 1.8 inhibition in neuropathic and nociceptive pain models.	[63, 64]
N-methyl-D-aspartate receptor	Activators- N-methyl-D-aspartate, glutamate, glycine, and Ca^{2+}; Inhibitors- Traxoprodil, ifenprodil, dextromethorphan, and	N-methyl-D-aspartate receptor implicated in central sensitization	Clinical data for lower affinity antagonists is conflicting; there is modest preclinical	[65, 66]

	memantine.	(both short and long term); N-methyl-D-aspartate receptor is ionotropic. glutamate receptors that are activated by severe or persistent nociceptive stimuli.	evidence for analgesia with N-methyl-D-aspartate receptor subunit 2B antagonists; glycine B antagonists have been proven in preclinical investigations to be effective for neuropathic pain.	
Transient receptor potential V1/ Vanilloid receptor 1	Activators- Resiniferatoxin, capsaicin; Inhibitors- A784168, AMG517,A795614, and AMG 9810	Transient receptor potential V1 channels are desensitized by agonists; transient receptor potential V1 are ion channels that are sensitive to membrane depolarization, temperature (>42°C), pH (6), and a wide range of ligands.	There is substantial evidence to support the use of topical agonists in the treatment of neuropathic pain; in preclinical research, antagonists give evidence for nociceptive and neuropathic pain; although clinical studies have been completed, no outcomes have been published.	[67, 68]
Mass oncogene-related gene receptor	Activators- BAM8-22, Tyr6-γ2-MSH-6-12.	Mass oncogene-related gene receptor activation suppresses postsynaptic	Evidence from nociceptive and neuropathic pain models in the preclinical stage.	[69]

		currents in the substantia gelatinosa *via* blocking N-type calcium channels in the dorsal root ganglion.		
Nerve growth factor inhibitors	Inhibitors- Tanezumab, fasinumab, ABT110, and REGN-475.	Nerve growth factor binds to tropomyosin receptor kinase A receptors on nociceptive nerve terminals, causing enhanced hypersensitivity and pain signaling.	In the neuropathic and nociceptive pain model, there is strong clinical evidence for humanized anti-nerve growth factor antibodies.	[70]
Tissue necrosis factor-α inhibitors	Inhibitors- Infiximab, etanercept.	During pain sensation, tissue necrosis factor-α triggers the growth factors and pro-inflammatory cytokines mediators.	In neuropathic and nociceptive pain model, strong evidence for tissue necrosis factor-α; supporting strong evidence against rheumatologic condition during the clinical stage.	[71]
Glial cell inhibitors	Inhibitors- SB203580, CEP-1347, D-JNKI-1, and propentifylline.	Peripheral nerve damage triggers glial cells, which produce inflammatory mediators that make	In neuropathic pain model, supporting strong preclinical evidence for glial cell inhibitor.	[72]

		nociceptive neurons in the area more sensitive.		
Nitric oxide and phosphodiesterase inhibitors	Inhibitors- NCX701.	The exact mechanism of pain sensation is unknown, though it may be dependent on the cyclic guanosine monophosphate signaling pathway being activated; analgesia from nonsteroidal anti-inflammatory drugs and opioids is enhanced.	Supporting strong findings when phosphodiesterase type 5 inhibitors are used with morphine; in preclinical models, fewer stomach lesions were shown with NO-linked treatments.	[73]
Bisphosphonates	---	The analgesic mechanism is unknown; it may work by inhibiting osteoclasts and having anti-inflammatory effects	Treatment for complex regional pain syndrome with low-quality evidence; strong clinical findings in situations characterized by increased bone turnover	[74]

Table 3: Toxins used as pain therapy in development.

Toxin	Species	Molecular target	Clinical stage	Manufacturer	References
Conantokin-G (CGX-1007)	*Conus geographus*	N-methyl-D-aspartate receptors, N-methyl-D-aspartate receptor subunit 2B	Phase II	Cognetix Inc.	[75]
Contulakin-G (CGX-1160)	*Conus geographus*	Neurotensin receptor	Phase II	Cognetix Inc.	[75]
ω-Conotoxin CVID (AM336)	*Conus catus*	N-type Ca^{2+} channels	Phase II	Zenyth Therapeutics	[76]
ω-conotoxin MVIIA (Prialt™)	*Conus magus*	N-type Ca^{2+} channels	Approved by FDA	Elan	[77]
α-Conotoxin Vc1.1 (ACV1)	*Conus victoriae*	Neuronal nicotinic acetylcholine receptors	Phase I	Metabolic Pharmaceuticals	[78]
χ-conotoxins Mr1A/Mr1B (Xen2174)	*Conus marmoreus*	Neruronal noradrenaline transporter	Phase I/IIa	Xenome	[79]
ρ-conotoxin T1A	*Conus tulipa*	α1-adrenoceptors	At preclinical stage	Xenome	[75]

Conclusion

A major problem for the future of pain treatment is the current gap between fundamental scientific research and the development of novel pain therapeutics. This conundrum is particularly challenging to solve when trying to find improved treatments for comorbid chronic pain conditions because: a) Animal ‘pain' models may not properly reflect complex clinical pain; b) Subjective pain experience is not assessed in animal behavioral testing; c) Preclinical data are inconclusive when it comes to the direction of novel analgesic research; d) Clinical trials frequently use overly-sanitized research participants, failing to capture the multifaceted effects of comorbid chronic pain. To recapitulate, pain research and management require a thorough grasp of the complicated mechanisms of pain. As a whole, the current review focused on the cellular and molecular processes that support the pain pathway. Furthermore, the pivotal classes of neurotransmitters involved in pain mechanism *viz* transduction, transmission, and regulation, as well as their locus and potential pharmacological effects, have been thoroughly explored. This could help worldwide researchers gain a better grasp of the pain topic and provide a useful and effective roadmap for future analgesic drug discovery.

Future perspective

Pain is seen as quite unpleasant, and it can be debilitating at times. Pain affects one's quality of life and limits productivity at work. As a result, pain therapy or management is critical in this context. Despite significant progress has been made in understanding neurobiological aspects of pain, more sophisticated research using modern tools and approaches is still required, which may pave the way for a deeper understanding of neurobiological pathways and the development of innovative therapeutics for pain management.

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