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Chapter 16

Analgesics: New Target and Sources

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Additional information is available at the end of the chapter

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Abstract

The aim of this chapter is to describe targets for analgesic drugs, including currently available target sites and possible future target sites for pain and information regarding analgesia for complete understanding of pain originating mechanism, pathways and related theories to recognize. This chapter fully describes methods for determination of analgesic effects of synthetic and natural substances by inducing pain in different models and methods of pain induction.

Keywords: pain, analgesics, targets, sources

1. Introduction

Pain is the measure of a cautious response against organ damage or unevenness in its capacities against conceivably unsafe stimulation. The rising pathway of pain incorporates the contralateral spinothalamic tract, lateral pons, mid brain to thalamus and at last, through the somatosensory cortex of the cerebrum that defines the zones, force and profundity of pain [1]. Pain is the most widely recognized experience reported by patients, and patient tension is a type of caution sign. It is an exotic and perceptual sensation, which causes enduring and enthusiastic condition of dangers associated with tension. Pain has numerous structures. It cautions against harm to the body, which is critical for maintaining a strategic distance from wounds and thus for survival. Pain not brought about by intense wounds can be insalubrious for the patient, or it can adjust a man's life, decrease the personal satisfaction and furthermore affect the patient's family. 'Pain' for the patient means malady and enduring, for the specialist, it is a side effect and for the physiologist, it is a sort of feeling that has its own particular anatomical and physiological framework which starts with the receptors and winds up in the cerebrum cortex. Feeling is a physical impression that can be affirmed by electrophysiological

techniques, however, by and by, it is just a subjective sensation. Its force and quality go under different inside and outer elements; in this way, the same boost can be experienced distinctively in various circumstances and substantial and psychiatric conditions. The method for accepting pain is extremely individual and differs every once in a while in the same person. The force of pain is hard to quantify, and an individual's impression of nuisance relies upon the individual's enthusiastic state, circumstances under which the pain was obtained and whether it is seen as an undermining signal [2–4]. Before we understand that something harms, there are various physiological procedures in our body. Painful stimuli must be passed rapidly, in (milli) seconds. Intense pain cautions about looming or following risk while continual pain causes the burdened part of the body, for example, an immobilized and unused appendage, expanding the chance for healing. A solitary and sharp stimulus to pain can vanish and most likely not leave a track. Pain progression can be supported and inhibited by the adaptive changes in the central nervous system due to the repeated stimuli. Sense of pain is modified by the synthesis and activation of many receptor systems along with synthesis of numerous compounds in the brain and spinal cord. In this complicated process, glial cells perform a significant role in the preservation of the pain, even after the pain stimulus is disappeared [5].

In the peripheral and central nervous system, pain can also be generated without receptors. This sort of pain is always a pathological pain which ascends due to injury to the nervous system, and it has an altered nature from physiological pain and clinical presentation. Therefore, it is important to distinguish receptor pain—nociceptive, physiological pain from non-receptor pain—pathological, central and peripheral. In **Table 1**, different types of pain are defined.

Utilization of an intense harmful stimulus to ordinary tissue inspires intense physiological nociceptive pain. It shields tissue from being (further) harmed in light of the fact that withdrawal reflexes are typically inspired. Pathophysiological nociceptive pain happens when the tissue is excited or harmed. It might show up as unconstrained (pain without any deliberate incitement) or as hyperalgesia and/or allodynia. Hyperalgesia is a compelling pain force felt upon harmful incitement, and allodynia is the impression of discomfort inspired by stimuli that are ordinarily underneath pain edge. In non-neuropathic pain, a few creators incorporate the bringing down of the pain limit in the term hyperalgesia. While nociceptive pain is inspired by incitement of the tactile endings in the tissue, neuropathic pain results from harm or sickness of neurons in the peripheral or central nervous system. It does not essentially signal

Allodynia	Pain on account of a stimulation that does not customarily induce pain, e.g. pain brought on by a T-shirt patients with postherpetic neuralgia
Dysesthesia	An unpalatable anomalous sensation, whether unconstrained or evoked while paresthesia is not upsetting, e.g. in patients with diabetic polyneuropathy or lack of vitamin B1
Hyperalgesia	An expanded reaction to a jolt that is typically painful
Hyperesthesia	Expanded affectability to incitement, barring the exceptional senses, e.g. expanded cutaneous sensibility to warm sensation without agony/pain

Source: International Association for the Study of Pain.

Table 1. Types of pain.

noxious tissue stimulation and often feels abnormal. Its character is regularly smouldering or electrical, and it can be relentless or happen in short parts (e.g. trigeminal neuralgia), it might be consolidated with hyperalgesia and allodynia. Amid allodynia notwithstanding touching the skin can bring about serious pain. Reasons for neuropathic pain are various, including harm to central neurons (e.g. in the thalamus), axotomy, nerve or plexus harm, metabolic ailments such as diabetes mellitus or herpes zoster [6].

1.1. The nociceptive system

Nociception is the encoding and preparing of toxic boosts in the sensory system that can be measured with electrophysiological procedures. Neurons involved in nociception structure the nociceptive framework. Harmful boosts enact essential nociceptive neurons with 'free nerve endings' (Aδ and C strands, nociceptors) in the peripheral nerve. A large portion of the nociceptors reacts to toxic mechanical (e.g. crushing the tissue), warm (warmth or frosty) and substance jolts and in this manner is polymodal [7].

Nociceptors can likewise apply efferent capacities in the tissue by discharging neuropeptides (substance P (SP), calcitonin gene related peptide (CGRP)) from their tactile endings. Along these lines, they impel vasodilatation, plasma extravasation, attraction of macrophages or degranulation of mast cells and so on. This aggravation is called neurogenic inflammation [8].

Nociceptors and second-order neurons in the grey matter of the dorsal horn make synapses and nociceptors protrude towards spinal cord. A conscious pain response is produced due to the ascending axons of the second-order neurons and projection of brain stem or thalamocortical system upon noxious stimulation. Nociceptive motor reflexes include many spinal cord neurons that involve more unpredictable motor behaviour, such as hindrance in movements and generation of autonomic reflexes. The spinal nociceptive processing is reduced by descending tracts. These tracts are formed by pathways that originate from brain stem nuclei (in particular the periaqueductal grey, the rostral ventromedial medulla) and descend in the dorsolateral funiculus of the spinal cord. An intrinsic anti-nociceptive system involves this type of descending inhibition [9].

1.1.1. The peripheral pain pathway: primary afferent nociceptors

In skin, muscle and joint, numerous Aδ and C fibres thresholds have elevated for mechanical stimuli, along these lines going about as particular nociceptors that recognize possibly or really harming mechanical boosts. Mechano-receptors are fast-conducting Aβ afferents with corpuscular endings that react overwhelmingly to harmless mechanical boosts. An extent of Aδ and C strands results in warmth or frosty receptors encoding harmless warm and cold jolts yet not toxic warmth and cold. Notwithstanding polymodal nociceptors, joint, skin and instinctive nerves contain Aδ and C fibres that were named silent or initially mechano-insensitive nociceptors. These neurons are not enacted by harmful mechanical and warm boosts in typical tissue. Be that as it may, they are sharpened amid aggravation and after that begin to react to mechanical and warm jolts [10, 11]. This type of neurons produces enduring reaction to algogenic chemicals and also involved in intervening neurogenic inflammation in human beings [12]. They assume a

noteworthy part in starting central sensitization [13]. These neurons have unmistakable axonal biophysical qualities isolating them from polymodal nociceptors [11].

1.1.1.1. Peripheral neuronal mechanisms of neuropathic pain

When nociceptive field is stimulated, action potentials are generated in the sensory endings of healthy sensory nerve fibres. Pathological ectopic discharges are expressed in damaged nerve fibres. At the site of nerve damage or in the cell body of DRG, action potentials are generated. The released designs shift from recurrent terminating to irregular blasts [14, 15].

Ectopic releases happen in Aδ and C fibres and in thick myelinated Aβ fibres. In this manner, after nerve damages both low-threshold Aβ and in addition high-threshold Aδ and C fibres might be included in the era of torment. The procedures of central sensitization have been experienced by Aβ fibres that may inspire misrepresented reactions in spinal cord neurons. It was recommended that pain is not created by the impaired nerve parts themselves but instead by nerve fibres in the region of harmed nerve elements. After an exploratory sore in the L5 dorsal root, unconstrained activity potential releases were seen in C fibres in the uninjured L4 dorsal root. These filaments might be influenced by the procedure of a Wallerian degeneration [16].

1.1.2. Central pain pathways

1.1.2.1. The spinothalamic pathway

Dorsal root ganglia are a door to spinal cord for the entrance of nerve fibres where these nerve fibres impregnate around the spinal cord (dorsolateral tract of Lissauer) as 1–2 sliced parts and interact with the nerve cells in Rexed lamina I (marginal zone) and lamina II (substantia gelatinosa) then arrive the spinal grey matter. Substantia gelatinosa layer of the spinal cord is for the innervation of C fibres and marginal zone is for the innervation of Aδ fibres. These innervation of nerve cells is proceeded in the nucleus proprius (an area of spinal cord grey matter involving Rexed layers IV, V and VI), which remains continue to spinal midline then come up (in the anterolateral or ventrolateral part of the spinal white matter) through the medulla and pons and finally reaches the thalamus particular zone.

In this way, pain information and normal thermal stimuli (<45°C) are transmitted through spinothalamic pathway. The thalamic pathway encountering anomaly represents as a cradle of pain; this can be seen in patients with central pain or thalamic pain after stroke in the region of paralysis. In **Figure 1**, bradykinins, K^+ and prostaglandins are released by tissue injury thus stimulates nociceptors and subsequent release of substance P and histamine produce vasodilation and swelling.

1.1.2.2. The trigeminal pathway

Trigeminal ganglion and cranial nuclei VII, IX and X are the sites for the nerve cells to recognize the harmful stimuli through the nerve fibres where nerve fibres cross the threshold to the brainstem as well as medulla. Across the neural midline, these nerve fibres ascend to the contralateral side of the thalamic nerve cell. Trigeminal neuralgia is defined as the spontaneous firing of trigeminal nerve ganglion (In the positive results of Janetta's trigeminal decompression

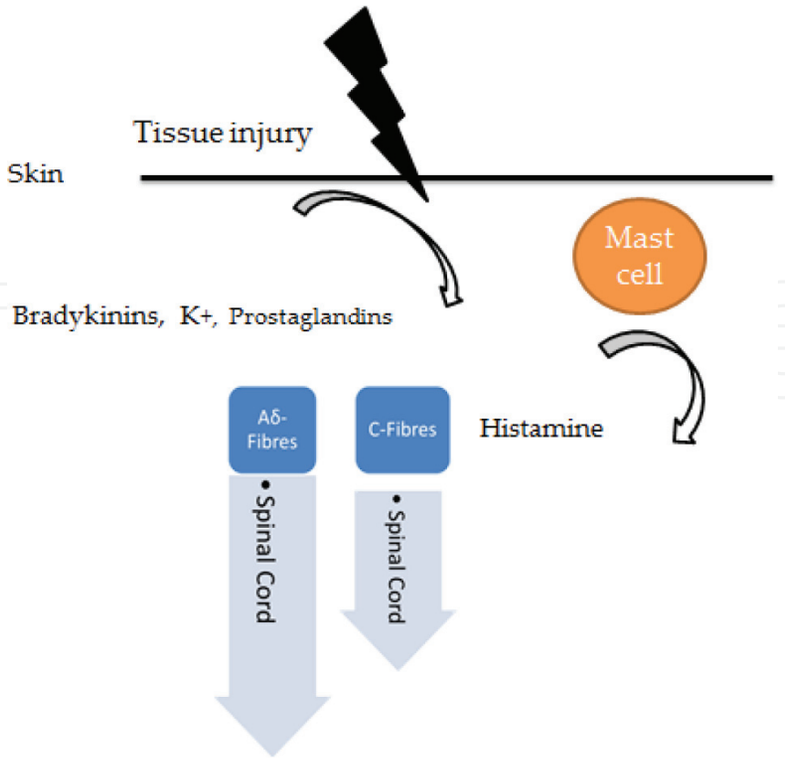

Figure 1. Nociceptor stimulation by tissue damage and vasodilation and swelling by the release of histamine (modified from Patel [17]).

surgery, cerebellar artery and local trigeminal nerve damage by mechanical lesion is thought to be cause).

The range of the thalamus that gets the pain data from the spinal cord and trigeminal nuclei is additionally the territory that gets data about normal sensory stimuli, for example, touch and pressure. From this territory, nerve fibres are sent to the surface layer of the cerebrum (cortical regions that arrangement with sensory data).

In this way, evidence on the area and the intensity of the pain can be handled to wind up a 'confined painful feeling' by having both the nociceptive and the normal somatic sensory information focalize on the same cortical territory.

In certain situations, e.g., after limb amputations, cortical representation may change into two types of painful ('phantom pain') and non-painful sensations ('telescoping phenomena') [18]. In **Figure 2**, the raphe nucleus provides serotoninergic (5-HT), and locus ceruleus provides adrenergic modulation. Therefore, selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (e.g., amitriptyline) may exhibit analgesic properties.

1.1.3. Pain theories

1.1.3.1. Specificty theory

In this theory, Descartes suggested that harmful and non-harmful perceptions can be distinguished by the decoding of specific pain fibres [19].

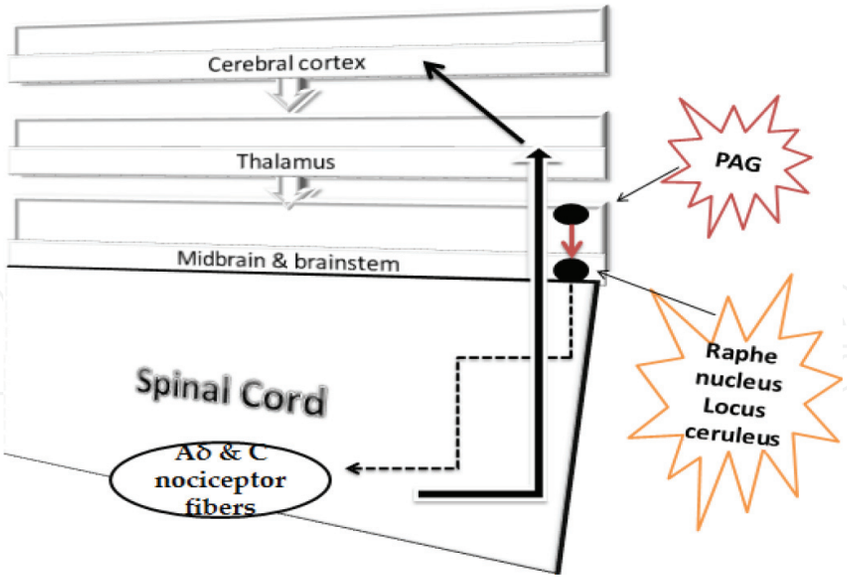

Figure 2. Serotoninergic (5-HT) and adernergic modulation by the raphe nucleus and locus ceruleus. PAG—periaqueductal grey matter, part of endogenous opioid system (modified from Patel [17]).

1.1.3.2. Intensity theory

Sydenham proposed that the peripheral stimulus acts as a signal whose intensity determines which type of sensation should be percieved [20].

1.1.3.3. Gate control theory

Melzack and Wall recommended that second-order spinal neurons (Dorsal horn transmission cell or wide dynamic range (WDR) neuron are stimulated by sensory fibers of divergent specificity that, unpredictably fire, subject to their degree of facilitation or inhibition. Inhibitory substantia gelatinosa (SG) cells are stimulated by large sensory fibres because in dorsal horn transmission cells are triggered by both large and small diameter afferents [21]. In the substantia gelatinosa, neuron and integrated circuits regulate the opening and closing of 'gate' [22].

Direct suppression of transmission cells by SG cells close the gate. On the other hand, the SG cells suppressive effect declines due to the amplified activity in small diameter fibres which can also be increased by the peripheral nerve damage and cause the opening of gate and also face decrease in inhibition of large fibres [23].

2. Target of pain: central and peripheral

2.1. Peripheral targets

At the peripheral terminal, pro-inflammatory mediators are released from the mast and schwann cells, macrophages and neutrophils which are resident and migrating cells, respectively, due to the injury to cells and blood vessels in return of stimuli, for example, a tissue damage or infection. Dorsal root ganglion (DRG) cells hold receptors for these mediators, which upon activation initiates a cascade of event from the intracellular kinases. In turn, receptor

phosphorylation causes the terminal sensitization, amplified afferent movement and stimulation at lower threshold.

2.2. Central targets

The spinal primary afferents due to cell insult, such as tissue injury, inflammation or nerve injury activate the primary afferents and induce voltage gated calcium cannels (CaV) and soluble N-ethylmaleimide-sensitive factor activating protein receptor (SNARE) Protein-dependent release of neurotransmitters, growth factors and neuropeptides. The resident glial and migrating cells (T cells, macrophages and neutrophils) in the spinal cord along with the second-order neurons are activated by the release of these substances, which in turn release a collection of pro-inflammatory and anti-inflammatory molecules to further act on the second-order neurons activating several protein kinases responsible for the phosphorylation of several membrane bound receptors, thus initiating and maintaining the hyperexcitable state of these neurons, and further sending the nociceptive signals to higher brain centres. The second-order neurons facilitate the excitability of dorsal horn projection neurons and scheme onto raphe-spinal serotonergic neurons through the bulbospinal pathway which dismiss in dorsal horn neurons [24]. In **Table 2**, central and peripheral pain targets are shown along with their source of cell insult/stimuli and inflammatory mediators and receptors which are and may be the future targets for pain alleviation.

2.3. Pain targets with molecular mechanisms of activation and sensitization of nociceptors

In **Figure 3**, Nociceptors direct ion channels for generation of transduction and action potential, and a large number of receptors for inflammatory and other mediators are either coupled to ion channels or, more often, activate second messenger systems that influence ion channels.

2.3.1. Transient receptor protein (TRP) channels

The transient receptor protein subfamily V member 1 is an individual receptor from the TRP (transient receptor protein) family. Other TRP individuals might be transducers of temperature boosts in different extents [26]. Capsaicin, the compound in hot pepper, opened the ion channel that grounds burning pain. Specifically, Ca^{2+} moves through this channel and depolarizes the cell. The TRPV1 receptor is opened by heat (>43°C) thus measured one of the transducers of noxious heat. In TRPV1 knock-out mice, the heat response is not eradicated but the mice do not display thermal hyperalgesia throughout inflammation, presenting the significance of TRPV1 for inflammatory hyperalgesia [27, 28]. Up-regulation of TRPV1 transcription during inflammation explains longer lasting heat hypersensitivity. The TRPV2 receptor in nociceptors is assumed to be a transducer for exciting heat (threshold >50°C). TRPA1 could be the transducer molecule in nociceptors reacting to frosty. It is actuated by impactful mixes, e.g. those present in cinnamon oil, mustard oil and ginger. By differentiation, TRPV3 and/or TRPV4 might be transduction molecules for harmless warmth in warm receptors and TRPM8 may transduce chilly jolts in harmless cold receptors. Despite the fact that the putative warmth transducer TRPV4 demonstrates some mechano-sensitivity, it is still in vague whether TRPV4 is included in the transduction of mechanical stimuli [29–31].

Type of targets	**Peripheral targets**		**Central targets**		
Stimulus	Tissue injury, inflammation or infection		Tissue injury, inflammation or nerve damage		
Source	**Local/resident cells**	**Migrating cells (Local/ DRG)**	**Resident cells**	**Spinal neurons**	**Migrating cells**
	Endothelial cells	Macrophages	Astrocytes		T cells
	Keratinocytes	Neutrophils	Microglia		Macrophages
	Mast cells	Bacteria			Neutrophils
	Schwann cells				
Inflammatory mediators and receptors	DNA, RNA, HMGB1 →	TLRs	**Pro-analgesics**	**Anti-analgesics**	
			Chemokines	**Cytokines**	
			CCL21	IFNy, IL-4, IL-10, IL-14	
			CCL2	**Lipid mediators**	
			Cytokines	Resolvins	
			TNF, IL-1β, IL-6	Protectins	
			Growth factors	Lipoxins	
			ATP	**Epoxy fatty acids**	
				Epoxyeicosatrienoic acids	
	FPS	FPR1	**Second-order neurons**		
	Bradykinins, 5-HT, CGRP, Prostaglandins, Lipoxygenases, proteinases	GPCRs			
			Protein kinases	Receptors	
	ATP	Purinergic Receptors	CaMK	NK-1	
	NGF, BDNF	TRK	PKA	NMDA	
	Chemokines (e.g. CCL2, CXCL1)	Chemokines Receptors	PKC	AMPA-CP	
	Cytokines (e.g TNF, IL-1β)	Cytokines Receptors	MAPK	mGluR1	
	sP	NK1		mGluR5	

Type of targets	Peripheral targets		Central targets
	H+	ASIC	P2X
	Lipids	TRPV1	GABA-A
		TRPA1	Glycine
			5HT3R

Source: Yaksh et al. [24].

Table 2. Schematic representation of peripheral as well as central targets from the point of insult to cells, sources of cell insult and inflammatory mediators and receptors for the current and future analgesics.

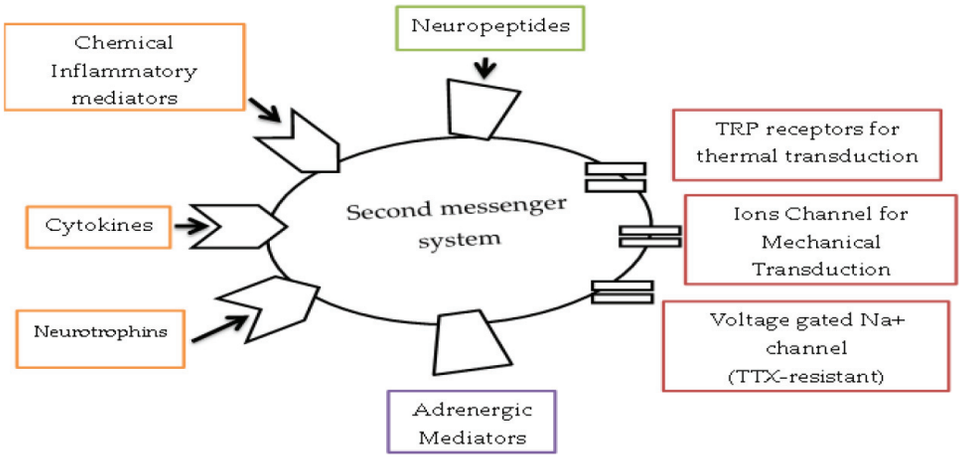

Figure 3. Ion channels for transduction of thermal and mechanical stimuli and action potential generation and metabotropic receptors subserving chemosensitivity involving sensory ending of nociceptor (modified from Schaible [25]).

2.3.2. Voltage-gated sodium channels and acid sensing ion channels

Tetrodotoxin (TTX) hindered many voltage-gated Na+ channels and numerous small dorsal root ganglion (DRG) cells direct TTX-resistant (R) Na+ channels, notwithstanding TTX-sensitive (S) Na+ channels. Both TTX-S and TTX-R Na+ channels pay to the Na+ influx during the action potential. Excitingly, inflammatory mediators pre-disposed TTX-R Na+ currents. Nociceptors are sensitized by boosted prostaglandin E2 (PGE2). This raises the likelihood that TTX-R Na+ channels likewise assume a part in the transduction procedure of poisonous boosts. SNS−/− knock-out mice (SNS is a TTX-R Na+ channel) show declared mechanical hypoalgesia, however just little shortages in the reaction to thermal incitements [32, 33]. Low pH values cause opening of acid sensing ion channels (ASICs) and are Na+ channels. In general, ASIC family comprises of six subunits (1a, 1b, 2a, 2b, 3, and 4). This is of interest because many inflammatory exudates exhibit a low pH. Protons straightforwardly initiate ASICs with ensuing generation of action potentials. The ASIC family expressed in peripheral neurons is ASIC 1b and ASIC 3 subunits which possess a high degree of selectivity in sensory neurons [34, 35].

2.3.3. Receptors of inflammatory mediators (chemosensitivity of nociceptors)

The chemosensitivity of nociceptors permits inflammatory and trophic intermediaries to follow up on these neurons. Inflammatory cells and non-neuronal tissue cells are their cradles. In the activation and sensitization of neurons, two types of receptors either ionotropic (the mediator opens an ion channel) or metabotropic (the mediator activates a second messenger cascade that influences ion channels and other cell functions) are encompassed. Numerous receptors are coupled to G proteins, which signal by means of the generation of the second messenger cyclic adenosine monophosphate (cAMP), cyclic guanosine monophosphate (cGMP), diacylglycerol and phospholipase C. The receptors are having intrinsic protein tyrosine kinase domains that associate with cytosolic tyrosine kinases and protein serine/threonine kinases [31, 36]. There are several functions of mediators, which may involve the direct activation of neurons (e.g. the bradykinin induces action potentials by itself) and/or sensitization of neurons for mechanical, thermal and chemical stimuli (e.g. bradykinin and prostaglandins increase the excitability of neurons so that mechanical stimuli arouse action potentials at a lower threshold than under switch circumstances occur). PGE2, for example, activates G protein-coupled EP receptors that cause an increase of cellular cAMP. This second ambassador actuates protein kinase A, and this pathway impacts ion channels in the membrane, prompting an improved edginess of the neuron with brought down limit and expanded action potential recurrence inspired amid suprathreshold incitement. Bradykinin receptors are of awesome interest on the grounds where bradykinin enacts various Aδ and C fibres and sharpens them for mechanical and warm boosts [37]. Freund's complete adjuvant induced mechanical hyperalgesia of the rat knee joints and thermal hyperalgesia can be reversed by the bradykinin receptor antagonists. A few reports recommend that specifically bradykinin B1 receptors are up-controlled in sensory neurons taking after tissue or nerve damage, and that B1 antagonist diminish**es** hyperalgesia. Up-regulation of B2 receptors during inflammation also found by some authors [38, 39].

2.3.4. Neuropeptide receptors and adrenergic receptors

Receptors for a few neuropeptides have been recognized in primary afferent neurons, including receptors for the excitatory neuropeptides SP (neurokinin 1 receptors) and CGRP, and receptors for inhibitory peptides, in particular for opioids, somatostatin and neuropeptide Y (NPY) [40, 41].

3. Current strategies for pain control

The treatment of constant pain ought to be multi-directional. There are pharmacological strategies for treatment, physical, rehabilitation, neuromodulation, psychological techniques and now and again, surgical methods. It is critical to guarantee careful and exhaustive nurture of the patient, and to elucidate and acquire acknowledgment of the picked strategy for treatment from the patient.

3.1. Pharmacotherapy

Pharmacotherapy should always be chosen independently be chosen exclusively, in light of the fact that what helps one individual does not as a matter of course help another, and may even be unsafe. The decision of medication ought to be founded on fitting finding and presently utilized pain relieving treatment. It is critical to consider conceivable symptoms which happened amid the past utilization of the medications. It is additionally critical to consider conceivable association of the proposed drug with different pharmaceuticals utilized by patient for different illnesses. To get a viable pain control, a blend of medications with various components of activity is utilized. They are additionally accessible as prepared details containing a mix of two or more active ingredients. In **Table 3**, some nociceptive conditions are described which can be managed by the drugs interfering neurotransmission.

3.1.1. Classification of Non-steroidal anti-inflammatory drugs

Currently used non-steroidal anti-inflammatory drugs with their mechanism of actions, indications, therapeutic advantages and disadvantages are listed in the **Table 4**.

3.2. Physical therapy and rehabilitation

A supporting technique is utilized as a part of the treatment of pain. The most well-known strategies for physical treatment are thermotherapy (heat), cryotherapy (cool), laser treatment, electrotherapy, manual methods, restorative concentrates and kinesiotherapy. These techniques, utilized as a part of a fitting way, may enhance life and portability of a few patients.

3.3. Neuromodulation

Neuromodulating treatments are aimed at stimulating the pain systems. Currently, several neuromodulation methods are used: percutaneous nerve electrostimulation (TENS), peripheral nerve stimulation, acupuncture and vibration. Neuromodulation supports pain treatment

Conditions	Pain management
Inflammatory states	NSAIDs, act on COX-1, COX-2 and opiate receptors
Nerve injury	Antidepressants, MAO Inhibitors, e.g. Amitriptyline, Duloxetine, Venlafaxine
Neuropathic pain	Sodium channel blockers (Lidocaine, Carbamazepine)
	Calcium channel blockers (Ziconotide, Gabapentin)
	Increasing extracellular level of inhibitory transmitter (GABA), e.g. Tigabin
	Opioids (lesser extent)
Topical medication for cutaneous allodynia and hyperalgesia	Lidocaine, Capsaicin

Source: Sinatra [42].

Table 3. Pain conditions and Current analgesics for pain management.

NSAID	Mechanism of action	Therapeutic advantages	Therapeutic disadvantages	Indications
Salicylates				
Aspirin	Irreversibly inhibit COX-1 and COX-2	Low cost; long history of safety	Upper GI disturbances are common	Fever, pain, anti-inflammatory and anti-platelet
Diflunisal			No anti-pyretic effect	
Acetic acids				
Indomethacin	Reversible inhibitors of COX-1 and COX-2		Upper GI disturbances are common	Anti-pyretic, analgesic, anti-inflammatory
			Very potent should be used only after less toxic agents have proven ineffective	
Sulindac		Long half-life permit once or twice daily dosing	Same as indomethacin but less sever	Fever, pain inflammation, RA, ankylosing spondylitis, osteoarthritis of hip
Propionic acids				
Ibuprofen	Reversible inhibitors of COX-1 and COX-2	Lower toxicity and better acceptance in some patients	Headache, patent ductus arteriosis, tinnitus, dizziness, prolong bleeding time	Fever, pain, anti-inflammatory, anti-platelet, osteoarthritis, rheumatoid arthritis
Fenoprofen				
Flurbiprofen				
Ketoprofen				
Naproxen		Naproxen is considered by some experts as one of the safest NSAID		
Oxaprozin		Long half-life permit once daily dosing		
Oxicams				
Piroxicam	Inhibits both COX-1 and COX-2, with preferential binding for COX-2	Long half-life permit once or twice daily dosing	GI disturbance in 20% patients	osteoarthritis, rheumatoid arthritis, ankylosing spondylitis
Meloxicam		Long half-life permit once or twice daily dosing	Less GI irritation than Piroxicam	
Fenamates				
Mefenamic acid			Diarrhoea, inflammation of bowel, haemolytic anaemia	
Meclofenamic acid				
COX-2 inhibitors				
Celecoxib	More selectively inhibit COX-2	Less GI irritation than aspirin	Potential for increasing myocardial infarctions	RA, rheumatoid arthritis, acute to moderate pain

NSAID	Mechanism of action	Therapeutic advantages	Therapeutic disadvantages	Indications
			and strokes, headache, diarrhoea	
Heteroaryl acetic acids				
Diclofenac	Selective COX-2 inhibitor	Employed in long-term therapy		osteoarthritis, rheumatoid arthritis, ankylosing spondylitis
Tolmetin				Anti-inflammatory, anti-pyretic, analgesic
Ketorolac			Fatal peptic ulcer, GI Bleeding, Perforation of the stomach or intestine	Moderate to Severe pain, moderate inflammation, allergic conjunctivitis

Source: Clark et al. [43].

Table 4. Classification of currently used Non-steroidal anti-inflammatory drugs along with mechanism and indications.

methods, and by activating the pain inhibitory mechanisms, one can reduce pain and improve the quality of life of patient with chronic pain.

3.4. Psychological therapies

Psychological factors have a big influence on the perception of pain, as well as the effectiveness of the treatment. Therefore, all patients with chronic pain should be able to take advantage of professional psychological help, which can affect the emotional aspect of pain. Among the psychological methods that can be effective as a technique supporting the treatment of chronic pain, the most commonly used are cognitive therapy, behavioural therapy, relaxation techniques and hypnotherapy.

3.5. Invasive methods

These procedures of pain management should be executed and administered by experienced specialists in specific cases. Numbers of methods are available, i.e. individual nerves block, intrathecal administration of drugs (e.g. epidural anaesthesia during childbirth) to neurodestructive

Scientific name/common name	Family	Parts used	Medicinal used	References
Berberis calliobotrys	Berberidaceae	Stem	Analgesic for Rheumatoid arthritis	[44, 45]
Manilkara zapota	Sapotaceae	Leaves	Analgesic	[46]
Clerodendrum phlomidis	Verbenaceae	Stem bark	Analgesic	[47]
Bach	Araceae	Rhizome	Analgesic	[48]
Ocimum suave	Lamiaceae		Analgesic	[48]
Lippia adoensis	Verbenaceae	flower	Analgesic	[48]
Ajuga remota /bugle	Lamiaceae		Analgesic	[48]
Pimpinella anisum	Umbellifera	Seeds	Narcotic analgesic	[49]

Scientific name/common name	Family	Parts used	Medicinal used	References
Myrtus communis	Myrtaceae	Leaves	Narcotic analgesic	[50]
Tribulus terrestris	Zygophyllaceae	Aerial	Narcotic analgesic	[51]
Sinapis arvensis	Solanaceae	Aerial	Narcotic analgesic	[51]
Withania somnifera	Solanaceae	Leaves and fruit	Narcotic analgesic	[51]
Peganum harmala	Zygophyllaceae	Whole plant	Narcotic analgesic	[51]
Hibiscus rosa sinensis	Malvaceae	leaves	Analgesic	[52]
Stylosanthes fruticosa	Papilionaceae	Whole plant	Analgesic	[53]
Polyalthia longifolia	Annonaceae	Leaves	Analgesic	[53]
Ficus glomerata	Moraceae	Bark and leaves	Toothache, analgesic	[53]
Baugainvillea spectabilis	Nyctaginaceae	Leaves	Analgesic	[53]
Toona ciliata	Meliaceae	heart wood	Analgesic	[53]
Sida acuta	Malvaceae	whole plant	Analgesic	[53]
Chococca brachiata	Rubiaceae	Root	Anti-inflammatory, analgesics	[54]
Bauhinia racemosa	Caesalpiniaceae	Stem bark	Analgesic	[54]
Casearia sylvestris Swartz. (wild coffee)	Flacurtiaceae	Leaves and bark	Anti-inflammatory, analgesics	[54]
Elephantopus scaber	*Elephantopus scaber*	Leaves	Anti-inflammatory, analgesics	[54]

Table 5. Some plant sources under study to develop new analgesics.

procedures (neurolysis, thermo lesion,) and neurosurgery. Advance medicine provides many different methods for the management of pain.

4. Plant sources of analgesics

Due to obvious adverse effect of synthetic drugs, herbal medicinal plants are focusing to develop newer analgesic agents with fewer side effects. Some plants having analgesic activity are given in **Table 5**.

5. Experimental models for screening of analgesic substances

The animal models employed for screening of analgesic agents include

5.1. Pain-state models using thermal stimuli

For the activation of cutaneous receptors, heat is a suitable stimulus. Nociceptive stimulation origin can be far apart from its target, for example radiant heat from a lamp in a direct touch

with the skin. Comparatively, radiant heat comprises a selective stimulus for nociceptors; moreover, it has an advantage of producing no tactile stimulus over the other ways of thermal stimulation.

5.1.1. The tail-flick model using radiant heat/immersion of the tail in hot water

It is one of the most simplified procedures used in human subjects with radiant heat [55]. In fact, Hardy et al. finally used this method in rats [56]. After the exposure to thermal radiation of the tail of an animal it takes out the tail by a brief dynamic movement [57]. This separation of the tail from the heat source is termed as 'tail-flick latency'. In this method, a timer is started at the time of application of heat and the time taken for the rat to withdraw its tail from heat source is recorded. Withdrawal time is usually within 2–10 s. It is advisable to not to lengthen the exposure to radiant heat more than 20 s as the skin of the tail may be burnt. In order to control the intensity of the current passing through the filament, a rheostat is inserted in the apparatus which further controls the intensity of radiant heat. Some investigators have used cold as a substitute of hot stimuli; this test can be used on monkeys as well. The use of immersion of the tail is apparently a variant of the test described above [58].

5.1.2. Paw-withdrawal test

This test is completely comparable to the test of D'Amour and Smith [59] but have the benefit that it does not involve the pre-eminent organ of thermoregulation in rats and mice, i.e. the tail [60]. In this test, a paw is exposed to radiant heat that had previously been swollen by a subcutaneous injection of carrageenan. By exposure to ultraviolet rays, inflammation can also be produced. Heat applied to a freely moving animal is an advantage of these types of tests [61].

5.1.3. Hot-plate model

In this test, a mouse or rat is presented into an open-ended cylindrical space with a floor composed of metallic plate that is heated by boiling liquid or a thermoderm [62]. Two behavioural components are produced by heating the plate at constant temperature that is calculated in terms of their reaction times, namely jumping and paw licking. In terms of analgesic chemicals, the paw licking behaviour is influenced only by opioids. On the contrary, by using less powerful analgesics, for example, paracetamol or acetylsalicylic acid, the jumping reaction time can be increased, especially when the temperature of the plate is 50°C or less or if the temperature is changing incrementally and in linear fashion, e.g. from 43 to 52°C at 2.5°C/min [63]. The behaviour is more complex in the rat and relatively stereotyped in the mouse like it sniffs, licks its forepaws, licks its hind paws, straightens up, and stamps its feet, starts and stops washing itself, among other things. These behaviours have been labelled 'chaotic defensive movements' [64].

5.1.4. Pain-state models using cold stimuli

For stimulation and measurement of pain in mice, a new animal model has been developed and designed. This laboratory model (M-model) basically consists of four parts (i) perspex-box,

(ii) M-Zone, (iii) ice-tray and (iv) ice floor. At the start, the mouse is exposed to different parts of the M-model mainly M-Zone for about 60 s, so that the mouse is sensitive of the existence of M-Zone prior to the initiation of the experiment. From the top/ceiling of the perspex box, the animal is inserted. The ice tray containing of ice block is slide onto the floor of the perspex box. When the animal is not able to bear the cold surface of ice floor, it escapes to M-Zone. The time taken by the animal to run away into the M-Zone (Flight-Zone) when placed on the ice-floor is called endurance time. This time is recorded with the help of a stopwatch. In general, mice take about 4–6 s to escape into the M-Zone to evade ice floor. Separate groups of animals are pre-treated with narcotics such as butorphanol (partial opioid agonist, 2 mg/kg, s. c), tramadol (opioid agonist, 5 mg/kg, s. c), pentazocine (10 mg/kg, s. c) and non-narcotic analgesics such as ketoprofen (non-selective COX inhibitor, 5 mg/kg, p. o), diclofenac (non-selective COX inhibitor, 15 mg/kg, i. p) and meloxicam (preferential COX-2 inhibitor, 5 mg/kg, s. c) to determine their effect on endurance time. This time is recorded at 0, 15, 30, 45, 60, 120 and 180 min after administration of the standard drugs [65].

5.2. Pain-state models using mechanical stimuli

5.2.1. Strain gauges

In this test, an increasing amount of pressure is applied to a punctiform area on the hind paw or, far less frequently, on the tail. The tail or paw is wedged between a plane surface and a blunt point mounted on top of a system of cog wheels with a cursor that can be moved in the direction of length of a graduated beam [66]. When the pressure increases, following step wise reactions occurs, i.e. the reflex removal of the paw or a complex movement of the animal to free its captured limb and at last a vocal response is noticed. Randall and Selitto with the aim of enhancing the sensitivity of the test offer comparison of thresholds seen with an inflamed paw and with a healthy paw [67].

5.2.2. von-Frey filaments

The key method for the study of pain in animal models is the assessment of mechanosensitivity. This is frequently executed with the use of von-Frey filaments in an up-down testing model. This is the most commonly used method for measuring pain in animals described by Vivancos [68] for mechanosensitivity testing in rodents. Though, in this method, animals are getting a changeable amount of stimuli which may direct the animals in distinctive groups getting diverse testing experiences that affect their subsequent responses. In order to standardize the measurement of mechano-sensitivity, a simplified up-down method (SUDO) for reckoning paw withdrawal threshold (PWT) with von-Frey filaments has been developed that uses a constant number of five stimuli per test [69].

5.3. Pain-state models using electrical stimuli

5.3.1. Electrical stimulation of the tail

Progressively escalating strength of electrical stimuli can be applied in range (lasting for some milliseconds) through subcutaneous electrodes positioned in the tail of the mouse or the rat. One can see the following: when such slowly increasing intensities of electrical stimuli are

applied from invariable voltages 40–50 V, i.e., the impulse movement of the tail, vocalization occurs at the time of stimulation, and then, utterance continuing ahead for the period of stimulation. Due to the electrical current, the animal may be died. Morphine or morphine-like drugs are useful in this model [70].

5.3.2. Grid-shock test

Approximately weighing of 18–20 g of male mice is put into the clear plastic chambers. The floor of box spaced about 1 mm apart is wired firmly with stainless steel wire. In the form of square wave pulses, the stimulus is given 30 cycles/s with a period of 2 ms/pulse. By escalating shock intensities, the mice gasp, show a frightening reaction, increase movement or effort to jump. Pain threshold response is defined as the behaviour correctly reflected on the oscilloscope by marked vacillation of the displayed pulse. Prior to administration of the test drug the pain thresholds are find out in each individual mouse twice at 15, 30, 60, 90 and 120 min subsequent dosing [71].

5.3.3. Stimulation of the tooth pulp

In this method, electric current is applied to stimulate the tooth-pulp of the animal. Pain symbol is exhibited as biting, chewing, licking and head flicking.

Rabbits of either sex are used as animal model. Thiopental 15 mg/kg or fentanyl-citrate 0.2 mg/kg i.v. produces anaesthesia. A high-speed dental drill is used to create pulp chambers in the lateral margins of the two front upper incisors.

Rectangular current with a frequency of 50 Hz for 1 s is applied. The 0.2-mA electrical current produces the phenomenon of licking [72].

5.3.4. Monkey-shock titration test

This model carries monkeys as animal model and kept them in restraining chairs. The monkey shock titration is a final evaluation of a new compound before administration to man. Electrical current is conveyed by a Coulbourn Instrument programmable stunner through cathodes coupled to two test tube clasps, which are connected to a shaved bit of the tail. The current ranges from 0 to 4 mA through 29 progressive steps. This current is suppressed by a bar pressed by monkey. On the day before the drug administration, a stable baseline shock level is recognized for each monkey. Drugs in different doses like 3.0 mg/kg i.m. morphine, 1.7 mg/kg i.m. methadone, and 10 mg/kg i.m. pentazocine were used. However, this test is time consuming [73].

5.3.5. Stimulation of the limbs

For pharmacological studies of analgesia, electromyographic recordings of nociceptive limb reflexes have been used for, but they are far less common than behavioural tests. These electromyographic studies have permitted the measurement of reactions paying little heed to whether there is any development.

5.4. Pain-state models using chemical stimuli

The experimental models in which chemical stimulation is done with the administration of algogenic agents represent an irreversible, slow, and progressive form of stimulation, which are nearby in nature to clinical pain.

5.4.1. Formalin test

The formalin test in rats, a chronic pain model is used to assess the centrally active analgesic agents. In this test, excessive licking and biting of the paw is recorded as response after the administration of formalin (37% solution of formaldehyde) into the front paw. Both paws resting on the floor indicated the analgesic response or protection of the test drug. The response as painful behaviour can be evaluated on a four-level scale related to posture: 0 represents normal texture; 1 represents the injected paw not supporting the animal but leftovers on the ground; 2 represents animal raised up the injected paw visibly; and 3 represents animal shows responses like licking, nibbling or shaking of injured paw [74].

5.4.2. Acetic acid induced writhing test

In this method, pain is indicated as a characteristic behaviour of contraction of abdominal muscles and stretching of hind paws along with twisting of dorso-abdominal muscles, and motor in co-ordination in rats or mice (called writhing) after the administration of allogenic agents like phenyl quinone or acetic acid into the peritoneal cavity which irritate the serous membrane; therefore, this test is called 'writhing test'. These writhings are counted as per unit of time [74].

5.4.3. Stimulation of hollow organs

In hollow organs such as rat colon, formalin is injected, and a complex biphasic type of 'true visceral pain' is exhibited in two phases. In first phase, contraction and stretching of body and in second phase, abdominal licking and nibbling behaviour is shown by the animal. Intravesical administration of capsaicin or turpentine produce bladder pain, glycerol produces abdominal constrictions and intrauterine injections of mustard oil show complex behaviour patterns in a number of models including rats. Another mean of stimulus for colorectal distension in rat is an inflatable balloon [75, 76].

6. Conclusion

The ASIC family is a potential target for new analgesics. In rheumatoid arthritis and vascular ischemia, as well as in the routine perioperative settings, inflammation and ischemic pain conditions are a sign mark of acidic nociception which can be reduce by the NSAIDs and by direct inhibition of sensory neuron ASIC current [77].

Work is currently in progress on a more selective and potent ASIC blocker and could potentially be an effective agent in the treatment of inflammatory and ischemic acute or chronic pain in the future [78]. Key regulators of membrane excitability are inflammatory mediators and key receptors (kinins, mPGEs), ion channels (TRPV1, NaV 1.7), and neurotrophins (NGF).

Similarly, α(2A)-adrenoceptor agonists also proven to be effective in various pain conditions, in the spinal dorsal horn, by inhibitory action on α(2A)-adrenoceptors on central terminals of primary afferent nociceptors (presynaptic inhibition), by direct α2-adrenergic action on spinal pain-relay neurons (post-synaptic inhibition) noradrenaline released from descending pathways originating in the pontine A5–A7 cell groups decreases pain and by α1-adrenergic activation of inhibitory interneurons. Furthermore, α(2C)-adrenoceptors on axon terminals of excitatory interneurons might subsidize to spinal control of pain [79]. These targets are currently under work to establish new analgesics with minimum side effects as exhibited by the currently used COX inhibitors.

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