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REVIEW

Multifactorial pathways in burn injury-induced chronic pain: novel targets and their pharmacological modulation

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Abstract

Burn injuries are among the highly prevalent medical conditions worldwide that occur mainly in children, military veterans and victims of fire accidents. It is one of the leading causes of temporary as well as permanent disabilities in patients. Burn injuries are accompanied by pain that persists even after recovery from tissue damage which puts immense pressure on the healthcare system. The pathophysiology of burn pain is poorly understood due to its complex nature and lack of considerable preclinical and clinical shreds of evidence, that creates a substantial barrier to the development of new analgesics. Burns damage the skin layers supplied with nociceptors such as NAV1.7, TRPV1, and TRPA1. Burn injury-mediated co-localization and simultaneous activation of TRPA1 and TRPV1 in nociceptive primary afferent C-fibers which contributes to the development and maintenance of chronic pain. Burn injuries are accompanied by central sensitization, a key feature of pain pathophysiology mainly driven by a series of cascades involving aberrations in the glutamatergic system, microglial activation, release of neuropeptides, cytokines, and chemokines. Activation of p38 mitogen-activated protein kinase, altered endogenous opioid signaling, and distorted genomic expression are other pathophysiological factors responsible for the development and maintenance of burn pain. Here we discuss comprehensive literature on molecular mechanisms of burn pain and potential targets that could be translated into near future therapeutics.

Keywords Burn Injury · Chronic Pain · Nav1.7 · Transient receptor proteins · Mitogen-activated P kinase

Introduction

According to the International Association for the Study of Pain (IASP), pain is "an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage" [1]. It is a protective phenomenon that alarms the living system against any potential tissue damage. Burn injury is one of the most critical conditions worldwide which can lead to death of the patient [2]. It is the fifth most common cause of non-fatal childhood injuries. According to WHO, an estimated 11 million burn injuries occur worldwide with approximately 1,80,000 death counts (https://www.who.int/en/news-room/fact-sheets/detail/burns). In India, over ten lakhs of people suffer from burns every year [3]. The majority of burn injuries occur in children with the most common causative factors including flames or exposure to the hot liquid [4]. After severe burning rapid diagnosis, appropriate initial burn resuscitation and treatment are required, unavailability of that can cost the life of the patient. Both physical suffering like edema, inflammation, and emotional suffering including post-traumatic stress disorder (PTSD) and depression, are associated with burn injuries. Burn injury is classified into three types based on the severity of the injury, among them third-degree burns known as full-thickness burns are the most severe causing the maximal damage by penetrating to the deeper body tissues. As the full-thickness burn injury penetrates deeper tissues, it sensitizes the nociceptors, further leading in the development of neuropathic pain. [5]. The neuropathic pain is mainly attributed to direct stimulation of nociceptors located in the two distinguished layers of skin namely the epidermis and dermis. In the peripheral nervous system, pain signal travels

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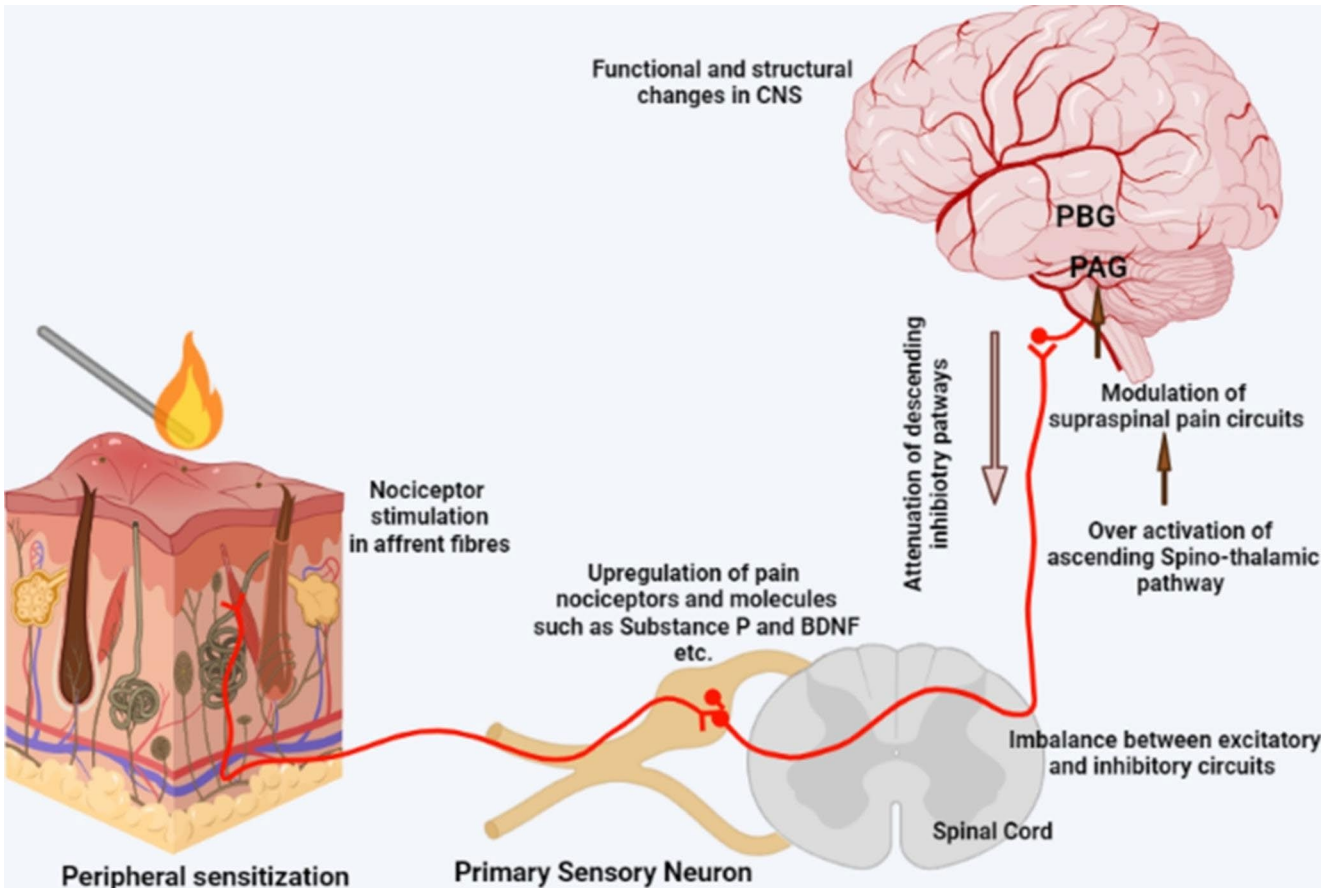

Fig. 1 PNS to CNS processing of burn induced pain. Peripheral stimulus (burn) causes damage to the nociceptors underlying the layers of skin which initiate a series of cellular cascades. This in turn transmits the signals to DRG and reaches the dorsal horn of spinal cord. Further the signal reaches to the higher brain regions via ascending pathways. Pathogenesis of chronic pain occurs due to the imbalance in excitatory and inhibitory spinal and supraspinal circuits

across the Aδ and C fibers and reaches the relay center of the pain pathway, the spinal cord [6]. From the dorsal horn of the spinal cord, the signal travels to the supraspinal brain regions where it gets interpreted. Both peripheral stimuli and descending pathways from the CNS are responsible for the magnitude of impulse transmission (Fig. 1 [7]. This series of events result in persistent hypersensitivity to a thermal and mechanical noxious stimulus. At present, it remains a challenge to manage burn injury-induced pain due to the unavailability of effective treatment devoid of severe side effects [2]. Moreover, poor understanding and complexity of burn injury-induced pain pathophysiology also creates a substantial barrier to the drug development. In this review, we have discussed the detailed insights into the cellular and molecular mechanisms associated with burn injury-induced chronic pain and the near future therapeutic targets for the treatment of the same.

Role of ion channels in pathophysiology of burn injury-induced pain

TRPV1 and TRPA1 crosstalk in burn injury-induced chronic pain

Two well-known transient receptor potential (TRP) cation channels namely TRPV1 (vanilloid 1) and TRPA1 (ankyrin 1) are responsible for the detection of various noxious heat stimuli. In burn injury TRPV1 is one of the most studied transient receptors which is activated by a temperature above 43 °C and additionally through the diverse forms of noxious stimuli that lead to the development of thermal hyperalgesia[8]. Studies have found that the enzymatic oxidation at the burn injury site releases endogenous ligands that stimulate TRPV1 which result in exhibiting thermal allodynia [9]. Even though TRPV1 nociceptors are activated by heat, it is not the sole player in heat-induced hypersensitivities. In a recent study double knockout of TRPV1 and TRPM3 in a mice model only showed moderate impairment in heat responses. In a mice model, it was established that, TRPV1,

TRPM3, and TRPA1 triple knockout (TKO) resulted in absence of response to acute noxious heat stimuli which was mandatory for avoiding burn injury-induced pain [9, 10]. Although the TKO mice showed a certain degree of insensitivity toward noxious heat stimuli, still normal nociceptive responses to mechanical and cold stimuli were intact. This proves that TRPA1 is yet another TRP channel having an essential role in burn injury. A selective TRPA1 antagonism has also been reported to completely hinder Ca^{2+} influx in sensory neurons in response to noxious heat stimuli. TRPV1 and TRPA1 nociceptors are widely co-expressed on nociceptive primary afferent C-fibres. TRPA1 receptors are activated by bradykinin which is one of the important peptide released as a result of burn injury mediated by G-protein-coupled receptors [11]. Two important pathways involved in regulating the activity of TRPA1 by bradykinin are B2 receptor and phospholipase C (PLC) pathway [12]. Thermal hyperalgesia occurs when bradykinin directly sensitizes nociceptors in the dorsal root ganglion (DRG) neurons [13]. Phosphorylation of the protein kinase C (PKC), as well as presence of low pH and capsaicin, facilitates bradykinin-sensitized activation of TRPV1 nociceptors [14]. Linoleic acid is the most abundant polyunsaturated fatty acid found in human tissue. After a burn injury, the enzymatic oxidative pathway (e.g., cytochrome P450) and the linoleic acid metabolites lead to activation of TRPV1 and TRPA1 nociceptors [9], which ultimately results in thermal and mechanical allodynia (Fig. 2). Targeting these nociceptors and their trafficking to neuronal membrane through dual agonist and antagonists, siRNA-based therapies, could provide a better alternate to the management of burn injury induced chronic pain (Table 1). However, the intactness of normal nociceptive responses that protect us from tissue damage should be considered while testing such therapies.

Nav1.7 channel-mediated mechanisms of burn pain

Voltage-gated sodium channels (VGSCs) plays an important role in the transmission of action potential post-application of nociceptive stimulus [15]. Nav1.7, Nav1.8, and Nav1.9 are preferentially expressed in primary somatosensory afferents specialized to sense noxious stimuli [16]. Among all these sodium channels, Nav1.7 is known to have a critical role in pain signaling [17–19].Mitigation of pain may be accomplished by the loss of sodium channel subtypes, especially Nav1.7 expressions. The sodium channels are essentially linked to peripheral neurons and are associated with human monogenic pain disorders. Nav1.7 is expressed not only on the unmyelinated axons of DRG neurons but also on its cutaneous terminals, indicating that both the initiation and conduction of action potential are dependent on Nav1.7 channel activation. Small hairpin RNA attenuates mechanical and thermal pain by knocking down Nav1.7 in L5-DRG neurons in the burn injury animal model[15]. Also, the complete deletion of Nav1.7 in sensory neurons has resulted in impaired thermal nociception in various behavioural tests. When the inactivation of Nav1.7 channels was first found to cause insensitivity to pain in 2006 [20], a new field of research emerged focusing on Nav1.7 blockers as a potential analgesic but this area needs further exploration to establish this as a translational therapeutic target. Preclinical studies and clinical trials have shown that tetradotoxin (TTX) has an analgesic effect and it is under clinical trial for cancer-related neuropathic pain [21]. A report has suggested that TTX inhibits thermal hyperalgesia and mechanical allodynia after full-thickness burn injury in rodents [22].

Deciphering the immune system hoisting the burn mediated chronic pain

Inflammation as a critical mediator of burn injury-induced pain

Burn injury is accompanied by inflammation, triggering a series of inflammatory events which aggravate the pain in patients [23]. Various types of cytokines are released from the injured tissue site, which reaches the systemic circulation and travels toward the CNS. Some of the cytokines plays a major role in activating nociceptive sensory neurons thus developing and maintaining chronic pain. Among such cytokines, the most important one is Interleukin-6 (IL-6) which is popularly known to induce mechanical hyperalgesia and central sensitization after thermal injury [24]. In a burn injury rat model, the administration of intrathecal antisense oligodeoxynucleotide against glycoprotein 130 (gp130) showed decreased mechanical allodynia[25–27]. Blocking the release of IL-6 further attenuates the progression of thermal and mechanical hypersensitivity in rodents [28]. Another pro-inflammatory cytokine, IL-1β is highly expressed in nociceptive sensory neurons of DRG after peripheral nerve injury and was also reportedly increased in the plasma of burn patients [29]. IL-1β stimulates the production of substance P in glial and neuronal cells. Along with TNF-α, IL-1β hinders the synaptic transmission and promotes neuronal excitability in lamina II of the spinal cord [30]. TNF-α amplifies spontaneous excitatory postsynaptic current frequency whereas, IL-6 diminishes spontaneous inhibitory postsynaptic current frequency while, IL-1β performs both these actions. Mechanisms behind these responses are that IL-1β and TNF-α enhance NMDA- and AMPA-induced excitatory currents, on the other hand, IL-6 and IL-1β diminish glycine- and GABA-induced inhibitory currents [31]. IL-10 is an anti-inflammatory cytokine having

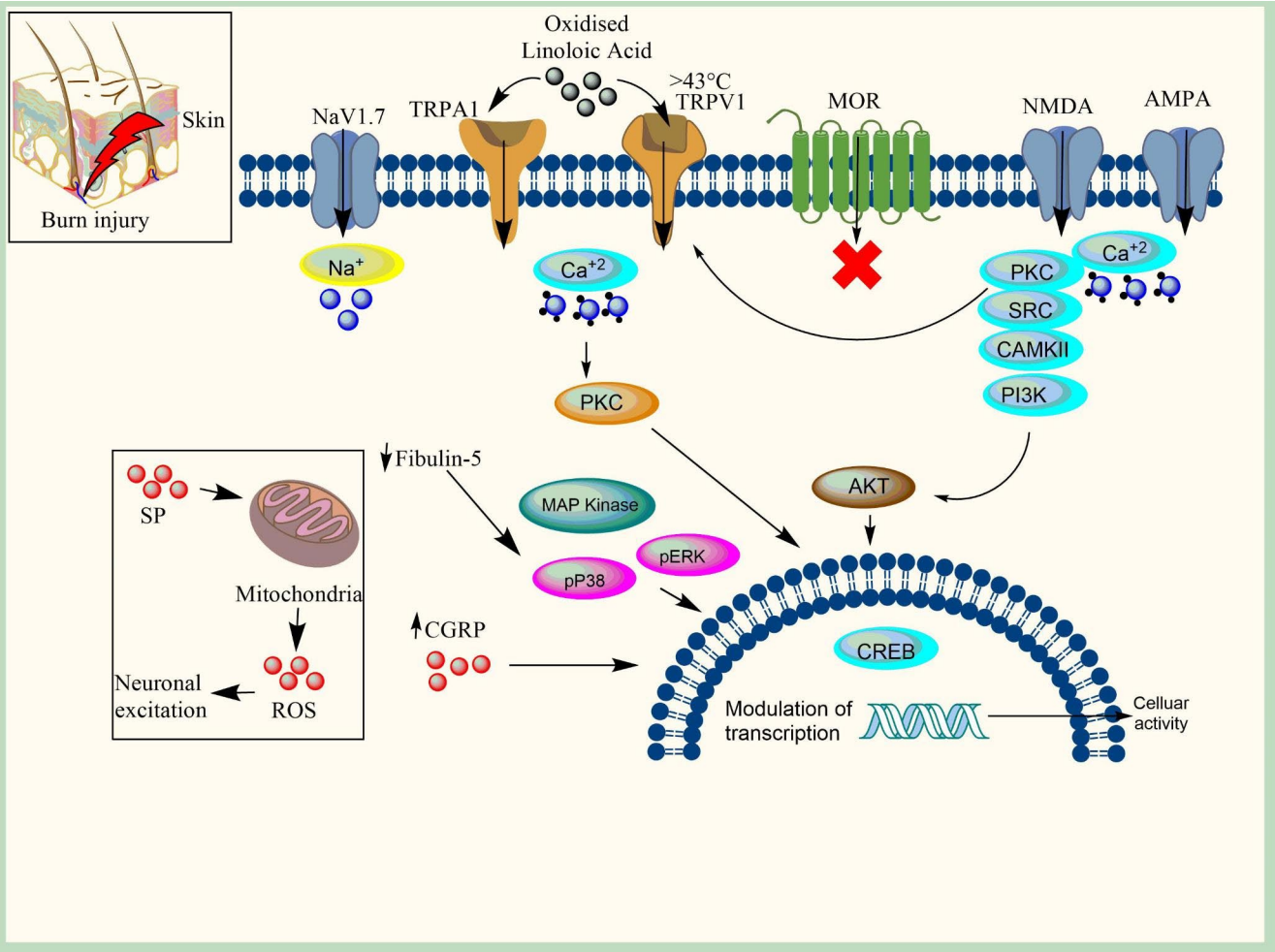

Fig. 2 Cellular mechanisms of burn induced pain. TRPV1 activates at a temperature above 43 °C, also by oxidized linoleic acid metabolites which are released after burn injury. Bradykinin produced after burn injury activates TRPV1 by PLC and PKC. TRPA1 are co-expressed with TRPV1. These two channels lead to increased pain transmission. Voltage-gated sodium channel (VGSCs) Nav 1.7 has a significant role in the induction of thermal nociception by the influx of sodium ions. From various elastogenic cells, fibulin-5 is secreted. After burn injury, its downregulation increases the expression of p-eIF2α, p-PERK which activate TRPV1 channel that ultimately results in the initiation of thermal injury evoked pain. Burn injury also activates P38 MAPK. The MAPKs signaling increases pain transmission through neuronal excitability. Burn injury results in the activation of the NMDA receptor followed by the opening of non-selective cation channels and lowers the pain threshold, followed by increased pain transmission

an inhibitory effect on the production of other inflammatory mediators including TNF-α [32]. For determining burn trauma and infections, the proportion of TNF-α and IL-10 in the plasma is taken into consideration [33].The response of nociceptive neurons can directly be altered by these inflammatory cytokines like TNF-α, IL-1β, IL-6, and IL-17. [34]. The frequency of C-fiber action potential is rapidly increased on administering the injection of these cytokines into the knees of the rat. [35]. This in turn leads to the sensitization of neurons transmitting pain signals.

Multi-protein complexes known as inflammasomes include nucleotide-binding oligomerization domain-like receptor protein (NLRP)-NLRP1, NLRP3, NLRC4, and Interferon-inducible protein (AIM2), which aggregate after various tissue damages or infections. NLRP3 is of particular interest because it plays a key role in the pathophysiology of autoimmune, inflammatory, and metabolic disorders [36]. The activation of the NLRP3 inflammasome leads to the secretion of caspase-1 (commonly known as interleukin-1 converting enzyme), which converts interleukin (IL)-1β into its active form [37]. Peripheral administration of IL-1β leads to mechanical and thermal hypersensitivity [38]. Thus, NLRP3 inhibition might provide a potential and novel therapeutic strategy to treat burn pain.

Table 1 Pharmacological targets for the management of burn pain

Target	Description	Functions	Activation factors	Manifestations	References
I) TRPV1 Channel	Calcium permeable ion channel belongs to the TRP category	TRPV1 is responsible for detection of various type of noxious stimuli and in pain transmission	Temperature > 43°C, Endogenous and Exogenous physical & chemical stimuli	Thermal hyperalgesia	[9, 13]
			Oxidized linoleic acid metabolites (OLAMs)	Thermal and mechanical allodynia	
II) TRPA1 Channel	TRPA1 is a member of the transient receptor potential channel family, a protein that is encoded by the *TRPA1* human *gene*	TRPA1 is co-expressed with TRPV1 on C-fibers which plays an important role in pain conduction	Bradykinin,	Hyperalgesia	[9, 11, 13, 67]
			Oxidized linoleic acid metabolites (OLAMs)	Thermal and mechanical allodynia	
III) Fibulin-5	Fibulin-5 is a glycoprotein that is encoded by *FBLN5* human gene	Fibulin-5 has an important role in fibers formation, also helps in wound healing by stimulating type I collagen expression and granulation tissue formation	After thermal injury Down-regulation of Fibulin-5 secreted by elastogenic cells, activation of TRPV1 occurs	Burn injury induced Inflammatory pain.	[56, 57, 59]
IV) P38 MAPK	P38 MAPK is member kinase family important for proinflammatory cytokines production in response to stress stimuli	MAPKs signaling has an important role to regulate inflammatory feedback	Burn injury activates MAPK. This activation is negotiated by PKA and PKC	Pain Mediation	[49, 50, 52, 53, 88, 95]
V) Substance P(SP)	SP is a Neuropeptide	SP acting as a neurotransmitter, a potent vasodilator and as a neuromodulator	Substance P with glutamate respond to noxious stimuli	Transmission of pain signal to CNS	[73, 74]
VI) Calcitonin gene-related peptide	CGRP belongs to the peptide of the calcitonin peptide family	CGRP has a role in the transmission of nociception. Also, in the formation of new vessels like in case of inflammation or wounds healing process	CGRP gene expression is regulated by the MAPK signaling pathway	Pain transmission in CNS	[78][59]
VII) Nav1.7	$Na_v1.7$ is one of the major VGSC which is encoded by the *SCN9A* human gene	Plays a crucial role in action potentials generation and transmission. Thus, important for electrical signaling by most excitable cells	Action potential caused by noxious stimuli	Burn-induced hypersensitivity	[17, 19]
VIII) μ-opioid receptors (MORs)	The μ-opioid receptors (MOR) are a class of GPCR opioid receptors	Mu opioid receptors (MOPRs) has the crucial role for modulation of pain and analgesia	Endogenous and exogenous opioids activate MORs. After burn injury reduced MOR expression occurs due to PKC activation which down-regulates the MOR mRNA expression	Analgesia	[81, 83]
IX)Glutamatergic signaling	NMDA Receptor, Kainate Receptor, and AMPA Receptor belong to this family	Involvement and activation of Calcium-permeable AMPA/KA receptors induce spinal sensitization	By the activation of NMDA receptor results to the entry of cation ions and lowers the pain threshold	Induce spinal sensitization and allodynia	[60, 69, 70, 106]

Microglial activation during burn pain

Microglial cells play an important role in the development of chronic pain by stimulating the release of IL-1β, IL-6, TNF-α, and BDNF, as a result of the inflammatory vicious cycle [39, 40]. These mediators participate in developing the central sensitization and pain symptoms. Microglia also expresses receptors associated with pain signaling such as AMPA, mGlu, and purinergic receptors [41]. Burn injury results in the damage of the peripheral nerve which further leads to the activation of neurons, releasing pro-inflammatory mediators. Damage to primary afferent neurons results in the production of colony-stimulating factor-1 (CSF-1) which further induces microgliosis and promotes the manifestation of pain [42]. All these changes can be reversed by administering CSF-1 inhibitor into the spinal cord. Investigations have shown that phosphorylation of p38 MAPKs is highly specific to spinal microglia, and is responsible for pain hypersensitivity and mechanical allodynia [43, 44]. Pain and related hypersensitivities have also been shown to be attenuated by inhibiting ERK 1/2 pathway and Rho-associated protein kinases (ROCK). Metalloproteinase-9 (MMP-9) is another factor which upon inhibition has shown to decrease microgliosis and mechanical allodynia.

Minocycline, a tetracycline derivative antibiotic has proven to decrease burn pain by inhibiting the microglial cells, thereby downregulating the production of proinflammatory cytokines [42, 43]. A recent report has suggested that burn-induced microglial activation occurs due to motor neurons residing ventral horn of the spinal cord [46]. Toll-like receptors (TLRs) family is also known to have an important role both in burn pain and innate immune response. Microglial activation is associated with TLR-4 -dependent signalling [47]. Studies have shown that TLR-4 knockdown in mouse model has shown to attenuate thermal hyperalgesia and mechanical allodynia [47]. Moreover, the administration of TLR4 antagonists in mice has been reported to reverse thermal hyperalgesia and mechanical allodynia [48]. Although the microglia represent a quality target for the management of burn pain, its surveillance role in CNS must be taken into consideration which could be altered after its blockade.

Role of P38 mitogen-activated protein kinase in burn-induced pain

The P38 mitogen-activated protein kinase (MAPK) plays a key role in the induction of proapoptotic genes after burn injury which manifest inflammatory responses [49]. It is considered as stress-induced kinase which upon activation facilitates gene transcription of proteins which leads to peripheral and central sensitization. P38 MAPK is not only involved in the development but also in the maintenance phase of chronic pain. In response to burn injury P38, MAPK is immediately activated in the spinal dorsal horn along with ERK1/2 phosphorylation [50]. The activated P38 MAPK expression is generally localized to lamina II neurons of the spinal dorsal horn, microglia, and oligodendrocytes [51]. Pain and related hypersensitivities are attenuated by inhibition of the ERK $_{1/2}$ pathway and Rho-associated protein kinase (ROCK). Protein kinases such as MAPK-APK-2/3 are phosphorylated by P38 MAPK resulting in the amplification of intracellular inflammatory signalling (Fig. 2). Tactile allodynia often accompanies a burn injury and is triggered by AMPA/kainite receptor activation. Investigations on P38 MAPK have reported its important role in AMPA/kainite receptor-mediated pain behaviour. In vivo treatment with P38 MAPK inhibitors has been shown to prevent the development of tactile allodynia in burn injury mice model [43]. Burn injury induces significant thermal and mechanical hyperalgesia which is attenuated by administeringp38 MAPK inhibitor [45, 52]. In burn injured mice, topical application of p38 MAPK inhibitor decreased the levels of inflammatory markers such as IL6, IL1β in the plasma and skin further preventing [53] organ failure. [54]. TNF-stimulated gene 6 protein (TSG-6), a potent anti-inflammatory protein is secreted by human umbilical cord mesenchymal stem cells that modulate the inflammatory response [55]. The tissue repairing process is enhanced in some animal models by the effect of TSG-6 on pro-inflammatory cytokine cascades. After burn injury, the protective and anti-inflammatory effect of this protein is regulated by inhibiting the stimulation of the P38 MAPK signaling pathway [56]. Though inhibition of P38 MAPK has been shown to exert relief in burn pain in different models, but for the ongoing role of P38 MAPK in mechanical hypersensitivity, it is hard to state the development role, also sufficient evidence has not been obtained from clinical trials for treating pain. Many attempts to achieve marketing authorization for a p38 MAPK inhibitor for the treatment of pro-inflammatory diseases, like rheumatoid arthritis (RA), and chronic pain failed at the state of clinical trials, mostly due to selectivity and/or toxicity issues.

Fibulin-5 a new player in burn injury mediated nociception

The extracellular matrix (ECM) is necessary for tissue homeostasis, embryonic growth, and physiological remodelling, which is composed of structural proteins, glycoproteins (matricellular proteins), tissue growth factor, etc. Recently the fibulin family has attained special interest for its comprehensive role in cellular physiology, also has a necessary role in the stabilization of macromolecular ECM complexes [57]. Fibulin-5 is a 66-kDa glycoprotein secreted by various cells type including vascular smooth muscle cells, fibroblast and endothelial cells. Fibulin-5 contributes to the formation of elastic fibers by binding to structural components including tropoelastin and fibrillin-1, and to cross-linking enzymes, aiding elastic fiber assembly which further contributes in the wounds and injury [58]. The elevated Fibulin-5 in the granulation tissue after full-thickness injury in mice negotiates endothelial cell adhesion by ligation of integrin and promotes collagen expression in dermal wounds [59]. Thus fibulin-5 is a novel promoter of wound healing that stimulates type-I collagen expression and granulation tissue formation [60]. According to a new study, Fibulin-5 overexpression in the DRG tissue of burn injured mice reduces the inflammatory response and, as a result, relieves pain. Interestingly, it also inhibits TRPV1 channel function and the CREB/CGRP signaling pathway by downregulating eIF2 phosphorylation. [61]. Screening of novel pharmacological compounds that can upregulate the fibulin-5 expression can provide a new direction for dual targeting by promoting would healing and mitigating pain hypersensitivities.

Glutamatergic signaling and central sensitization during burn pain

Glutamate is the major excitatory neurotransmitter across the neurons of the dorsal horn of the spinal cord. The release of glutamate occurs in response to nociceptive stimulation and tissue or nerve injury[62, 63]. The glutamate and its receptor have a significant role in the integration and perception of nociceptive signals. Glutamate acting via the NMDA receptor system induces central sensitization which is a primary feature of chronic pain [64, 65]. It has been found that following a burn damage, glutamate receptors are overexpressed. Taking this thing into account, inhibition of NMDA receptors will mitigate burn injury-induced hyperalgesia and central sensitization [66]. Gabapentin is also reported to act by inhibiting the presynaptic NMDA receptors involved in the central sensitization during chronic pain[67, 68]. Gabapentin has established efficacy in the reduction of burn-induced hyperalgesia and allodynia in animal and human experimental burn models [68, 69]. Human burn models also result in an area of surrounding hyperalgesia and allodynia that can be suppressed with oral gabapentin but not placebo [72]. Both the animal and human experimental burn models confirm that following a burn injury, there is a resultant development of secondary tactile allodynia and hyperalgesia qualities often attributed to neuropathic pain [71]. The recommended dose for the management of burn pain is 300 mg tds with titration if necessary up to 3600 mg/day. Children start at 10 mg/kg with titration 40–50 mg/kg [66, 67]. Selective NMDA antagonists are usually preferred as it reduces pain and shows lesser side effects. Inhibition of glutamate release in animal models has been shown to attenuate hyperalgesia and allodynia from noxious stimuli. Moreover, burn injury-mediated development of secondary hyperalgesia is reduced by AMPA receptor inhibition[74, 75]. Similar to the NMDA receptor, activation of AMPA/kainate receptors enhances burn pain behavior, while antagonists reduce the noxious stimulation[76]. Additionally, studies have shown to diminish secondary hyperalgesia and central sensitization in burn models by CNQX or NBQX AMPA/kainite antagonists [77]. The mGlu receptors are also involved in the later phase of nociceptive responses as an increase in their expression is observed post-burn injury [78]. In contrast, numerous studies are indicating that group 2 mGlu receptors activation reduces hypersensitivity to thermal stimuli. These receptors along with vesicular glutamate transporters can cause significant changes in the downstream effects of glutamate and thus, modulate pain accordingly. In a clinical study the wind-up phenomenon in burn injury-induced pain disappeared 15 min after ketamine (NMDA antagonist) administration, but it reappeared after 45 min [79]. Henceforth, there is a need of conducting future studies recruiting glutamate receptors so that a better understanding can be developed for the pathophysiology of burn pain.

Neuropeptides signaling associated with burn injury-induced pain

Different studies reveal that neuropeptides can participate in different types of inflammatory responses which are associated with normal wound healing. In case of burn injury, neuropeptides including substance P and calcitonin gene-related peptide (CGRP), are secreted from central and peripheral neuron terminals [80]. These two peptides directly act on venules to produce vasodilation, which results in the spreading of edema. Substance P is synthesized in DRG and from there it travels towards peripheral sensory neurons and enhances vascular permeability [81]. Substance P is known to exert neuro-modulatory effects on nociceptive processing as it can mediate the activation of the NMDA receptor. In lamina I neurons of the spinal cord, substance P plays an important role in the processing and transmission of pain [82]. The release of glutamate and substance P can lower the pain threshold resulting in hyperalgesia. Moreover, substance P activates phospholipase C exacerbating excitatory response to glutamate actions in dorsal horn neurons in the spinal cord and thereby facilitating pain signal transmission [83]. Substance P also causes NMDA-mediated inward currents in DRG neurons and enhances long-term potential generation [84]. In non-neuronal immune cells, substance P exhibit a critical role in the expression of chemokine and their migration. These factors have also been observed as mediators of persisting pain [85]. On other hand, the CGRP plays a role in angiogenesis by affecting human endothelial cells in case of inflammation or wound healing. CGRP expression in neurons is found to be vital for transmitting nociceptive signals from the parabrachial nucleus to the central nucleus of the amygdala [86]. The Expression of CGRP is around 40–50% in DRG neurons and mostly in the C fibers. The nerve endings of the sensory neurons releases CGRP, leading to vasodilation and neurogenic inflammation. TTX-resistant Na^+ channels are expressed on small- to medium-sized nociceptive primary afferent neurons which are predominantly affected by the inflammatory mediators and are of great importance as CGRP repeatedly binds to the small to medium sized DRG neurons. It has been observed that the resistant effect of tetrodotoxin (TTX) on sodium current density is also enhanced by the effect of CGRP in sensory neurons [87]. In burn patients, basal levels of these two neuropeptides are observed to be significantly higher than in the control subjects [88]. These growing pieces of evidence suggest the significant role of substance P and

CGRP in increased pain perception as well as in peripheral sensitization which can be served as a potential target for the treatment of burn injury.

Opioid receptor signaling in burn-induced chronic pain

Mu-opioid receptors (MORs), a member of the endogenous opioid system, have a crucial role in the modulation of pain and analgesia [89]. Unlike other amino acid and monoamine neurotransmitters, opioid peptides and their conjugate receptors are expressed throughout pain pathways. Studies have suggested the presence of opioid receptors specifically, MORs and delta-opioid receptors (DORs), on unmyelinated peptidergic DRG neurons [90]. Peripheral injuries are known to induce spinal long-term potentiation often resulting in hyperalgesia and tactile allodynia [91]. In such cases, MOR agonists have not only been found to inhibit synaptic transmission but also to attenuate spontaneous ongoing pain [92]. Similarly, in the dorsal horn of the spinal cord, decreased levels of MORs were observed in rats with burn pain [93]. A possible explanation for this could be that the burn injury led to activation of PKC followed by the release of intracellular Ca^{2+} as well as initiation of intracellular cascades including heteromers formation, receptor internalization which cause down-regulation of surface MOR expression [94, 95]. In a burn injury-induced pain model, Zhang et al. studied the spinal antinociception induced by endogenous mu-opioid receptor (MOR) agonists. [49]. Their results showed that the phosphorylation levels of extracellular signal-regulated kinase 1/2 (ERK1/2) and p38 mitogen-activated protein kinase (p38 MAPK) in ipsilateral spinal cord tissues were significantly up-regulated after burn injury. Intrathecal injection of endorphins selectively inhibited the activation of p38 MAPK post burn injury. Further studies found that repeated application of the specific p38 MAPK inhibitor SB203580 dose-dependently inhibited burn-injury induced pain [49]. As opioids possess enormous side effects thus it's better to opt for recent approaches such as targeting peripheral opioid receptors [96]. Furthermore, targeting MORs in DRG by peripherally restricted agonists have been reported to cause analgesic effect without any neurological side effects [97, 98]. Such therapies could be developed for the management of burn pain with effective methodological approaches.

Role of melatonin and BDNF signaling in burn pain

In case of burn injury, oxidative stress has been markedly reported due to the synthesis of reactive oxygen species and free radicals. Melatonin being an indoleamine molecule is known for its free radical scavenging and anti-oxidative properties as it restores the glutathione levels in cell by crossing morphophysiological barriers including skin. Melatonin may also suppress the free radical generation by facilitating the synthesis of adenosine triphosphate. Thus, melatonin is a potential candidate for providing protective effects against oxidative damage caused by burn injury. Furthermore, melatonin has been found to regulate pain perception via its receptors MT1/MT2 and simple diffusion [91, 92]. In CNS, epithalamus, thalamus, and dorsal horns of the spinal cord are the main regions where MT1 and MT2 receptors are majorly expressed [101]. Melatonin antinociceptive effects are achieved by modulating the burn pain signaling across the descending pathway and also by decreasing BDNF levels [102]. MT2 mediates the inhibition of cyclic adenosine monophosphate (AMP) accumulation and the downregulation of intracellular Ca^{2+} diacylglycerol, and arachidonic acid. BDNF is an important modulator within the CNS and spinal BDNF signaling has been found to regulate nociceptive transmission and central sensitization [99, 100]. During chronic pain, the increased expression of BDNF in the spinal cord is observed [103]. It has also been demonstrated that BDNF is produced by spinal microglia in chronic pain conditions. Any insult to peripheral sensory neurons leads to ATP release which further mediates $P2\times4R$ activation, ultimately resulting in the production of BDNF [104]. Tropomyosin receptor kinase B (TrkB) in the spinal cord is activated by BDNF causing the elevated intracellular flow of Cl^- ions [105]. This results in potentiation of synaptic GluN2B-NMDAR currents and firing of action potential in lamina I neurons of the spinal cord. Also, an increase in BDNF production along with other inflammatory mediators has been reported upon activation of p38 MAPK [106]. Henceforth, there is a need for further evaluation of the melatonin receptors along with a better understanding of the role of BDNF in anti-nociception.

Future therapeutic targets for burn pain

After burn injury, altered expression of various genes is observed in the DRG neurons. Transcriptome analysis has suggested the involvement of neuropeptide Y (Npy), CCK 2 receptor (Cckbr), etc. genes in burn injury-induced pain. The up-regulation of Npy in pain models is responsible for the enhanced transmission of the nociceptive signal to the

spinal cord [107]Among the pain-related proteins, cholecystokinin 2 receptor (Cckbr) upregulation occurs after burn injury, which is responsible for reducing the effectiveness of opioids. Moreover, proglumide, a CCK receptor antagonist reverses the burn-induced mechanical allodynia [108].After an injury to sensory neurons, the expression of Interferon regulatory factor-8 (IRF-8) is increased in the spinal microglia and thus contributes to the development of chronic pain by activating various genes involved in the inflammatory response [109]. Suppression of IRF-8 in spinal microglia has been reported to reverse tactile allodynia. The corticotropin-releasing factor (CRF) receptors (CRFR1 and CRFR2) are expressed across the central pain pathways [26]. The upregulation of CRFR2 gene expression in the spinal cord is observed with burn pain conditions [27].Studies have concluded that activation of the AMPK receptor and NF-κB are involved in stimulating inflammatory pain. Suppression of this transcriptional factor NF-κB has hence been reported to cause analgesic effect in inflammatory pain by downregulating IL-1β expression [110]. On the other hand, a receptor that controls IL-1β production is enhanced cannabinoid type 2 receptor by inhibiting NLRP-3 inflammasome [111]. Injury to peripheral sensory neurons often leads to the activation of spinal microglia which often results in a significant increase in Src phosphorylation that further contributes to the development of chronic pain [112]. Administration of Src inhibitors in the spinal cord has shown to reduce ERK activity and reversal of mechanical allodynia in mice [112]. Lyn, a member of the Src family is especially known to activate ERK in chronic pain conditions and knockout of Lyn reduces the pain hypersensitivities specifically the tactile allodynia [113]. Another factor involved in chronic pain is cathepsin S and inhibiting this protease has proven to suppress the microglial activation and attenuate mechanical allodynia in rodents [114, 115].

Conclusions

The pain can persist for a longer period after the injury, sometimes for many months to many years. Currently available analgesics in the clinic does not provide adequate pain relief and exerts several unwanted side effects as well. Hence it becomes prudent to understand the complex pathophysiological mechanisms associated with burn-induced chronic pain and develop the novel therapeutics devoid of serious side effects. In this review, we have discussed the potential molecular pathways like CREB/CGRP pathway, p-38 MAPK signalling, and neuroinflammation in burn injury-associated pain. The activation of neuropeptides like substance P and CGRP also occurs along with stimulation of cation channels such as TRPV1, TRPA1 and NAV1.7 during burn-induced chronic pain. Distinct opioid signalling is observed in burn pain patients accompanied by altered genomic profiling, fibulin-5 expression and melatonin signalling. These series of events promote the central sensitization that finally contributes towards the pathophysiology of burn-induced chronic pain. We also discussed various kinases and proteases that are involved in burn-induced pain. Further, we highlighted the pros and cons of targeting peripheral opioid receptors for the management of burn pain. In a nutshell, we conclude that there are several new players which plays an important role in the development and maintenance of burn injury-induced chronic pain. Future in-depth studies are required to carry these targets from preclinical to clinical setup so that burn pain can be treated effectively without causing any serious side effects and toxicities in patients.

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Declarations

Competing interests Authors have none to declare.

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