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REVIEW

Intercellular communication and ion channels in neuropathic pain chronicization

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Abstract

Background Neuropathic pain is caused by primary lesion or dysfunction of either peripheral or central nervous system. Due to its complex pathogenesis, often related to a number of comorbidities, such as cancer, neurodegenerative and neurovascular diseases, neuropathic pain still represents an unmet clinical need, lacking long-term effective treatment and complex case-by-case approach.

Aim and methods We analyzed the recent literature on the role of selective voltage-sensitive sodium, calcium and potassium permeable channels and non-selective gap junctions (GJs) and hemichannels (HCs) in establishing and maintaining chronic neuropathic conditions. We finally focussed our review on the role of extracellular microenvironment modifications induced by resident glial cells and on the recent advances in cell-to-cell and cell-to-extracellular environment communication in chronic neuropathies.

Conclusion In this review, we provide an update on the current knowledge of neuropathy chronicization processes with a focus on both neuronal and glial ion channels, as well as on channel-mediated intercellular communication.

Keywords Connexin · Glia · Gap junction · Neuropathic pain · Neurodegeneration

Abbreviations

Ca_v	Voltage-gated calcium channels
CCI	Chronic constriction injury
CNS	Central nervous system
Cxs	Connexins
DRGs	Dorsal root ganglions
ECF	Extracellular fluids
GJs	Gap junctions
HCs	Hemichannels
ICF	Intracellular fluids
K_v	Voltage-gated potassium channels
Na_v	Voltage-sensitive sodium channels
SNL	Spinal nerve ligation
TTX	Tetrodotoxin

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Introduction

Neuropathic pain is a debilitating condition of the somatosensory nervous system triggered by nerve lesions, frequently associated with different pathologies including cancer, diabetes, infection or autoimmune disease, in which chronic pain sensitivity is pathologically amplified [1]. Chronic neuropathic pain states show peripheral and/or central sensitization, resulting in exaggerated perception of painful stimuli [2, 3]. A typical characteristic of neuropathic pain is stimulus-independent pain, a form of spontaneous pain often characterized by either persistent or paroxysmal pain perceived as stabbing or burning [2]. Alongside,

stimulus-evoked neuropathic pain, characterized by hyperalgesia and allodynia, frequently occurs after mechanical, thermal or chemical stimulation [4, 5]. Finally, neuropathies may be also associated with other sensory dysfunctions, such as dysesthesias, experienced as tingling or pricking sensations and may be intermitted or provoked by stimulation [4, 5].

During the early phase of neuropathic pain, neurons in superficial laminae of the dorsal horn of the spinal cord, which receive synapses from dorsal root ganglions (DRGs) sensory neurons, are triggered by numerous signals. In particular, studies published over the last decade have elucidated the role of central nervous system (CNS) resident glial cells in many aspects of pathological neuronal functioning, occurring in neuropathic pain [6]. Notably, during pathological painful responses or pain sensitization, microglia and astrocyte functions are altered and in turn mediate spinal microenvironmental modifications, throughout the release of soluble factors regulating nociceptive neuronal excitability [7–9]. Primary mechanisms in inducing such alterations are likely to be linked to sensory inputs to the dorsal laminae I–III. Such an astrocyte- and/or microglia-induced modification of the spinal milieu is recognized as a fundamental mechanism in mediating neuropathy chronicization processes [8, 9]. On the other hand, ectopic discharges, excitotoxic damage, trans-synaptic degeneration and neuronal suffering are known to exert a primary neurodegenerative insult, contributing to the development of central sensitization mechanisms [10–12]. Several evidences suggest that excitotoxic stimulation by DRGs neuron discharges induces a robust spinal sensory neuron degeneration in the late phase of the disease. Such pathological features are coupled with a reduction in inhibitory circuitry and dramatic changes in ion channels composition exacerbating central excitotoxic damage. Moreover, excitotoxic damage may be linked, at least partially, to reduced and/or impaired astroglial glutamate clearance efficiency [9, 13–15]. In this scenario, cell-to cell interaction and cell-to-extracellular environment communication are emerging as key factors in neurodegenerative disorders and chronic pain mechanisms, with a prominent role referable to Gap junctions (GJs), which represent the fundamental structures for the development and maintenance of physiological arrangement in several cellular activities, including cell signalling, differentiation and growth [16–20].

Mechanisms of chronicization during neuropathic pain

Lesions or diseases in neuropathic pain predominantly involve primary afferent unmyelinated C fibres, which terminate in upper laminae and myelinated mechanoreceptor Aβ and nociceptive Aδ fibres, projecting in deeper laminae of spinal dorsal horn [21]. Also, changes between central excitatory and inhibitory signalling occurs as a consequence of sensory nerve alteration in electrical properties, as well as signal transmission and either disinhibition or facilitation of mechanisms at the level of the spinal cord dorsal horn neurons. Particularly, increase of fibre firing or loss of inhibitory circuitry determines a state of hyperexcitability, ultimately leading to pain chronicization [22]. Hyperexcitability condition is shaped by functional rearrangements that considerably affect both interneurons and second-order nociceptive neurons and, importantly, intercellular communications and microenvironmental composition [22, 23].

The inhibitory components affected in the process of central sensitization include spinal resident inhibitory interneurons and the descending modulatory systems. The suppression of resident inhibitory circuitry induces a local unbalance finally resulting in a prominent excitatory stimulation. Information is then conducted to the thalamus, cortex and limbic regions, including cognitive and emotional components [24, 25]. Dysfunction of descending modulatory systems, primarily including periaqueductal grey matter, is also responsible for maintaining pain hypersensitivity [24, 25].

Primary afferent fibres form synapses with second-order spinal neurons, generating the ascending spino-thalamic tract and taking stimulation to the thalamus, whose neurons form synapses with third-order neurons that project to the cortex. Second-order nociceptive neurons, which convey sensory information to the brain, are the biological substrates establishing and sustaining central sensitization. An increased signalling due to phosphorylation of *N*-methyl-D-aspartate (NMDA) and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors, related to second-order nociceptive neuron changes, could explain the development of allodynia [26]. Second-order nociceptive neuron hyperexcitability is critically linked to a loss of GABAergic inhibitory circuitry at spinal level [27]. Altered neuronal circuitry and neurotransmission are closely related to ion channel rearrangement, influencing sensory transduction through the initiation and propagation of electrical signals and neuronal transmission along the axon from the periphery to the CNS [22, 28].

Voltage-sensitive ion channels regulate action potential and excitability of neurons via rapid, voltage-gated changes in ion permeability [29]. Besides ion selectivity through transmembrane pore, the most unique characteristic of these ion channels is the voltage-dependent activation linked to conformational changes mediated by electric field applied to the phospholipid bilayer. Their transient activation is regulated by transition to an inactive state, phosphorylation and receptor state [29]. Dysregulation of voltage-sensitive ion channels, in particular sodium, calcium and potassium

channels, holds a critical role in contributing to neuropathic pain chronicization.

Voltage-sensitive sodium channels

Voltage-sensitive sodium or Na_v channels are responsible for the depolarizing phase of the action potential [22]. A number of Na_v channels have been linked to the development of neuropathic pain, including $Na_v1.3$, $Na_v1.7$, $Na_v1.8$ and $Na_v1.9$ [30]. In particular, the tetrodotoxin (TTX)-sensitive $Na_v1.3$ channel is featured by fast activation and inactivation kinetics. $Na_v1.3$ rapidly produces persistent and depolarizing current increasing the excitability of cells. It is expressed at quite high levels during embryogenesis supporting and regulating development of neuronal circuits [31], but it is barely detectable in adult CNS [32–34]. High expression of this channel was detected in sensory nerve tracts and in spinal cord white matter, dorsal roots and deep laminae of the dorsal and ventral horn after axotomy and during neuropathic pain [35–38]. Given their localization, Na_v channels are strongly associated with neuropathic pain contributing to spinal hyperexcitability. The recent evidence in experimental models of neuropathic pain reported a down-regulation of $Na_v1.1$, $Na_v1.2$ and $Na_v1.7$ coupled with an up-regulation of $Na_v1.3$ expression in adult DRGs, thus suggesting a prominent role of $Na_v1.3$ during neuropathic pain conditions [34, 39, 40]. Notably, $Na_v1.3$ channels contribute to the development of spontaneous ectopic discharges and sustain typical firing rates of injured sensory nerves. Moreover, the TTX-sensitive $Na_v1.7$ channels, prevalently localized in sensory endings, are characterized by slow inactivation kinetics and fast activation with small depolarizing ramps [40, 41]. Indeed, in a rat model of spinal nerve ligation (SNL), a reduction of about the fifty percent of $Na_v1.7$ has been observed. Knockout model for $Na_v1.7$ has been reported to spontaneously develop allodynia [42]. In physiological conditions, $Na_v1.8$ channels are highly expressed in nociceptors; a robust $Na_v1.8$ reduction has been associated with neuropathy, while $Na_v1.8$ ablation reduces the development of mechanical allodynia and thermal hyperalgesia in a model of neuropathic pain [43]. $Na_v1.9$, a TTX-resistant channel, is prevalently localized in DRGs, nociceptive neurons and in C and Aδ fibres, with lower expression levels in large diameter Aβ fibres [44]. On one hand, experimental model of neuropathic pain reported a concomitant $Na_v1.9$ channel down-regulation in injured neurons, but little or no effect on neighbouring neurons and on thermal hyperalgesia and mechanical hypersensitivity [40, 45, 46]. On the other hand, Nav1.9-null mice have shown absent inflammatory hyperalgesia in response to inflammatory mediators [45, 47, 48]. As such, the role of Nav1.9 is likely linked to maintain inflammatory-induced hyperalgesia rather than inducing chronicization of neuropathic conditions (Fig. 1).

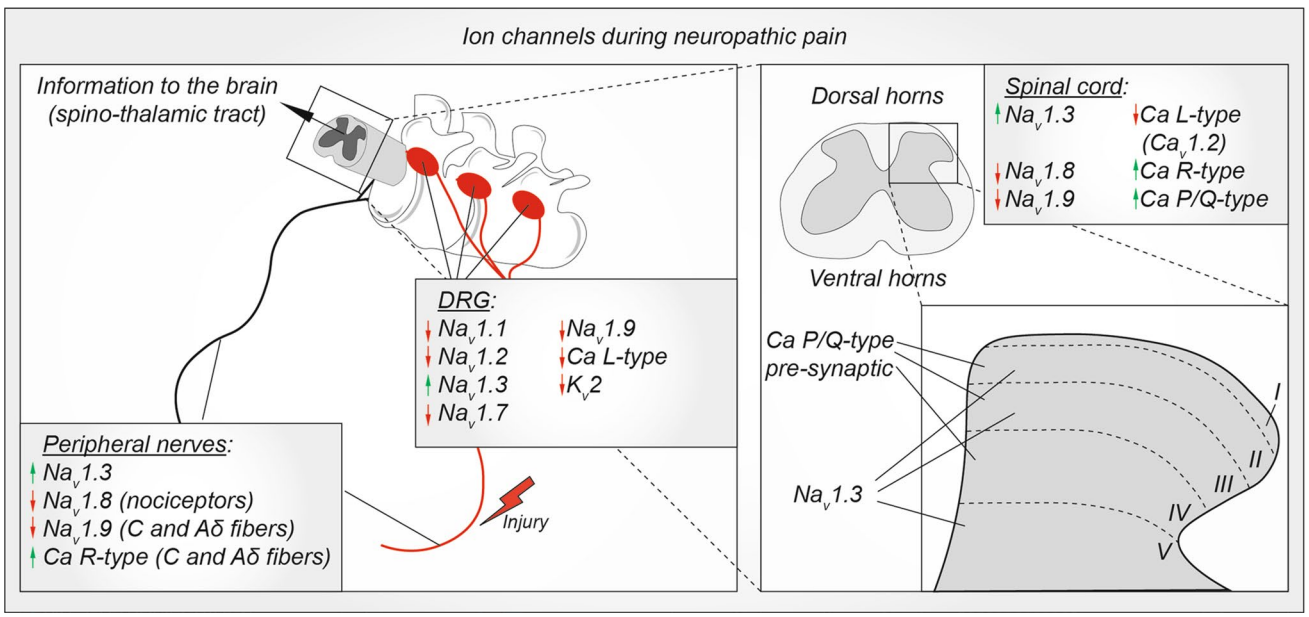

Fig. 1 Voltage-sensitive ion channels during neuropathic pain. Illustration of the localization and modulation (red arrows = decrease; green arrows = increase) of the main sodium (Na_v), calcium (Ca_v) and potassium (K_v) voltage-sensitive channels during neuropathic pain in the peripheral nerves, dorsal root ganglion (DRG) and spinal cord laminae I–V

Voltage-sensitive calcium channels

Calcium channels have been classified into low-threshold (T-types) and high threshold (L-, N-, P/Q- and R-types). Activation of voltage-gated calcium channels increases neurotransmitter release and enhances excitatory synaptic transmission in the nociceptive circuits [49]. L-type channels are distributed in neuronal cell bodies and dendrites of superficial laminae of the dorsal horn, where they mediate the activation of calcium-dependent enzyme activities, gene transcription, synaptic signalling and plasticity, as well as the activation of other ion channels, such as calcium-activated potassium channels [50]. In neuropathic pain models L-type channels are shown to be dysregulated in DRGs and in the spinal cord [50]. For example, some of their splicing variants, such as $Ca_v1.2$ and $Ca_v1.3$, are down-regulated in rat DRGs neurons following chronic constriction injury (CCI) of the sciatic nerve, while $Ca_v1.2$ is up-regulated in the spinal cord post SNL [51]. P/Q-type channels are expressed at the pre-synaptic terminals in the spinal dorsal horn, mainly laminae II–VI, where they play a role in neurotransmitter release. Their role in pain processing depends on the nociception aetiology [52]. In neuropathic pain models, P/Q-type channel blockade, as well as their deletion, resulted in no effect on mechanical allodynia and thermal hyperalgesia and in no changes in nociceptive responses to non-injurious thermal stimuli [52]. Calcium N-type channels are mostly distributed in DRGs cell bodies and in the synaptic terminals. The block of N-type current inhibits the release of substance P and calcitonin gene-related peptide (CGRP) from sensory neurons [53]. N-type channels are also widely distributed in spinal dorsal horn neurons, DRGs cell bodies and their central terminals, exerting a prominent role in pain transmission and processing. After peripheral nerve injury, these channels are up-regulated in spinal dorsal horn [54]. It has been demonstrated that intrathecal administration of ω-conotoxin, a modulator of gating properties, leads to a reduction of action potential-induced calcium influx by 50% without blocking the pore, reducing hyperalgesia and allodynia in neuropathic pain [55]. Analogously, it has been reported a reduction of nerve injury-induced allodynia by the potent N-type $Ca_v2.2$ inhibitor *N*-triazole oxindole TROX-1 [56]. R-type channels contribute to central sensitization in the spinal cord during neuropathic pain processing. Indeed, their blockade inhibits the neuronal responses of C and Aδ fibres in the dorsal horn and neuropathic pain states in nerve-injured rats. Moreover, up-regulation of $Ca_v\alpha_2\delta_1$ subunit, which is associated with L-type, N-type, P/Q-type and R-type calcium channels has been observed after peripheral neuropathy in DRG and in the dorsal horn of the spinal cord [57–60] and it has been related to the analgesic effects of gabapentinoids (Fig. 1) [61, 62].

Voltage-sensitive potassium channels

A family of ion channels involved in the sensory transduction machinery in DRGs neurons are the inhibitory voltage-gated potassium channels or K_v channels, mediating the repolarizing phase of action potentials. Since K_v conduction counteracts membrane depolarization and/or action potential, K_v activity generally inhibits sensory neuron excitability [63]. Recently, the crucial role in sensory transduction of K_v2 channels in DRGs was reported [64]. Indeed, reductions of K_v activity seem to be a hallmark of the hyperexcitability featuring neuropathic pain [65, 66]. Particularly, K_v2 channels regulate excitability of neurons, both in normal conditions and in neuropathic pain experimental models. A decreased expression of K_v2 channels has been observed also in preclinical models of neuropathic pain in the DRGs neurons of animals subjected to sciatic nerve axotomy [67] or CCI [68]. Although multiple factors are contributing to establishing excitotoxic and inflammatory milieu during chronicization processes of neuropathy, K_v channel function and expression in DRG neurons has been reported as a significant factor in inducing overactivation and persistent pain (Fig. 1) [69].

Role of non-selective gap junction and hemichannels

GJs are involved in direct intercellular communication and are characterized by the juxtaposition of two hemichannels (HCs) of adjacent cells, that allows the diffusional exchange of ions, metabolites (glucose, lactate and small metabolites) and second intracellular messengers (cAMP, IP3, ATP) between intracellular fluids (ICF) [70–72]. In addition, HCs themselves may actively contribute to alter extracellular fluids (ECF) and may individually act as membrane pore connecting ICF and ECF. GJs are aggregates in specific plasma membrane regions of adjacent cells forming GJ plaques, in which GJs are rapidly assembled, disassembled or remodelled [72]. HCs are added to the periphery of existing plaques and they are docked with HCs of adjacent cells, whereas old HCs are removed from the central portion of plaques to be destroyed [73, 74], with turnovers that are particularly rapid as compared to other membrane proteins. Each HC is composed by six subunits called connexins (Cxs), that arranging in a circle, delimit the central aqueous pore of HCs [16]. Cxs are a family of proteins encoded by 21 genes in human, each one named according to its theoretical molecular mass. Their molecular weight ranges from 26 to

56 kDa and some Cxs are selectively expressed in specific tissue and/or cell populations. Although their molecular weight is different, they have similar biophysical structures and features. Cxs are composed by four transmembrane domains, two extracellular loops, an intracellular loop and an intracellular carbo-tail [70]. Both homomeric and heteromeric HCs may constitute homotypic (same HCs) and heterotypic (different HCs) GJs. Despite such characteristics, the aqueous pore of the GJs has a diameter of about 2 nm and shows low ionic selectivity. It is widely accepted that GJs are preferentially in an open-state configuration, even if the gating is related to a rotation of the subunits which allows the pore formation. Cx43 is the most abundant Cx in mammals, widely expressed in glial cells from neurogenesis to adult brain. As the core glial GJ- and HC-forming protein, plays a leading role in physiological homeostasis of the nervous environment and injury [16, 75–77]. Cx43-composed GJs allow highly coupled intercellular network in CNS, interconnecting astrocytes but also mediating astrocytes–microglial cell coupling (Fig. 2) [78]. In particular, reactive astrocytes express high levels of Cx43 and increased Cx43-induced coupling in a number of acute and chronic degenerative affections of CNS [79–81]. Recent evidences support the hypothesis of a detrimental role of such a coupling that is believed to increase cell death signalling, as well as inflammatory and neurodegenerative insults [79].

Astroglial Connexin 43 sustains central sensitization during chronic neuropathy

Several data suggest that aberrant excitability of dorsal horn neurons evoked by peripheral nerve injury might not be a consequence merely of changes in neurons, but rather of multiple alterations of glial cells, including astrocytes and microglia, which undergo morphological hypertrophy, proliferation and specific gene expression profile [82–86]. Astrocytes exert bystander effects on neurons modulating their Cxs profile, thus playing a crucial role in pathological conditions via a detrimental exchange of ion channels, metabolites and secondary messengers.

In particular, the release of astroglial mediators, increases the activity of nociceptive neurons, sustaining inflammation and neuropathy development and maintenance. GJs/HCs have been progressively investigated to clarify the detrimental transition from acute to chronic condition, invariably more complex to be treated [2]. The fundamental role of cell-to-cell and cell-to-extracellular environment signalling has emerged as promising target to develop chronically active therapeutic options [9, 87]. This scenario has been comprehensively reviewed recently [88], highlighting current evidences on GJs and pannexin channels interplay and on potential therapeutic efficacy as alternative options to opioid analgesia. Several data support Cxs involvement in the induction and maintenance of chronic pain, so that antinociceptive effects of various molecules modulating activity or expression of Cxs has been investigated in multiple chronic pain models [89, 90]. In particular, Cx43 is considered a triggering factor for disease chronicization in the

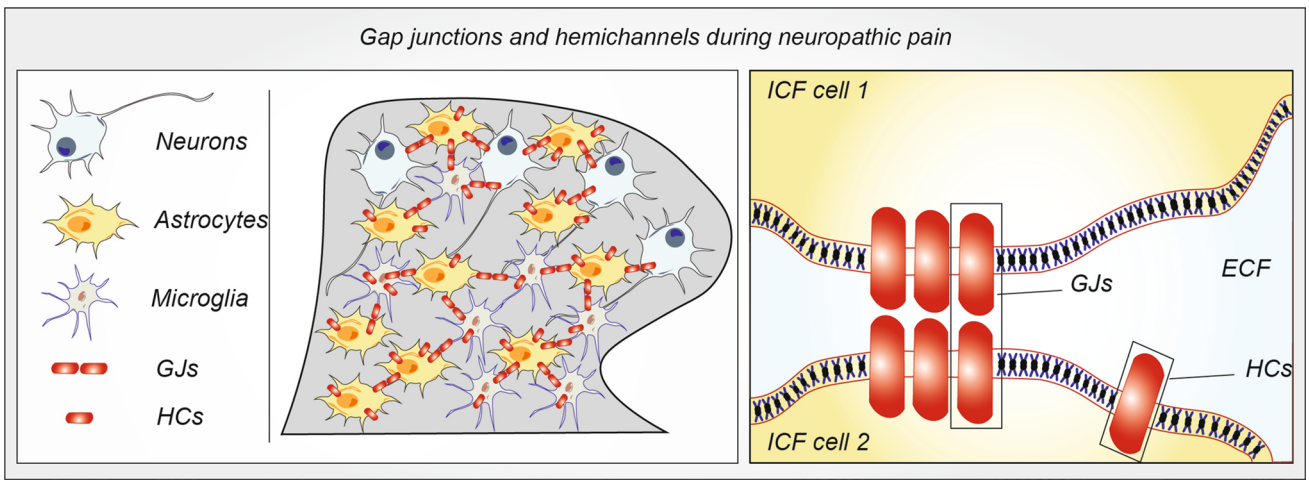

Fig. 2 Central sensitization mechanisms upon peripheral nerves injury. Illustration of spinal cell coupling underlying central sensitization involving resident spinal cord cells (astrocytes and microglial cells) and connexin-mediated cell coupling (gap junctions—GJs) and cell-to-extracellular communication mediated by hemichannels (HCs). Communication between cells (intracellular fluids—ICF—of cell 1 and cell 2) and between ICF and extracellular fluid (ECF)

CNS [5, 75]. Animal models of chronic pain, including CCI of the sciatic nerve, SNL, hind paw carrageenan-induced inflammation and unilateral hind limb bone cancer, showed astrocytic Cx43 protein overexpression in both the spinal dorsal horn, the sciatic nerve and the DRGs ipsilaterally to injury [76, 91–94]. Prevented nociceptive hypersensitivity through GJs blocker carbenoxolone and Cx43 RNA interference, further sustain Cx43 involvement along the pain pathway. Despite multiple evidences, the exact mechanism by which Cx43 acts, is still matter of debate. It has been described that astroglial Cx43 HCs mediate neuropathic pain by releasing chemokines in nerve sciatic-injured mice treated with peptide5, a Cx43 mimetic peptide that blocks HCs; it significantly improves mechanical pain hypersensitivity by selectively reducing ATP, which in turn determines reduction of the NOD-like receptor protein 3 inflammasome complex, a key mediator of neuroinflammation [76].

Over the years, dysregulated Cx43 and changes of Cx43-based GJs/HCs have been associated with CNS inflammation, including neurodegenerative and vascular diseases. Hallmarks of inflammatory conditions are reactive gliosis characterized by both astrocyte hypertrophy and proliferating astrocytes and microglia. In particular, degenerative stimuli occurring in other neurodegenerative diseases, such as in multiple sclerosis, Parkinson's disease, Alzheimer's disease and amyotrophic lateral sclerosis, are closely related to neuroinflammation and reactive glial cell response [95]. Such a phenomenon may represent either a triggering factor or a consequence of neuronal suffering and neurodegeneration. The overexpression of the Cx43 in several suffering conditions has been also investigated to establish whether it was cause or effect in the specific context. In the spinal cord, Cx43 expression is highly increased in both acute and chronic injuries, fostering inflammation and pro-apoptotic signalling [77, 96–98]. Particularly, evidences showed that inhibition of Cx43-based channels reduces secondary damages during acute and chronic disorders [78, 99]. As such, Cx43 up-regulation in spinal cord astrocytes is critical for the maintenance of late-phase neuropathic pain, but the specific role of Cx43 is still worthy of further investigation to find new therapies for chronic neuropathic conditions. Recently, an experimental model of neuropathic pain induced by the unilateral sciatic nerve CCI has been employed to investigate the effects of the multitarget biased mu and delta opioid receptor agonist LP2 [9, 100, 101]. In this context, the levels of astrocytic Cx43 in the spinal cord dorsal horn of CCI rats and its involvement in chronicization of neuropathy have been analyzed. Experimental evidence strongly supports the hypothesis of an active role of astrocytes in triggering pro-apoptotic signalling, fostered by Cx43 up-regulation in ipsilateral dorsal horn, that sustained chronic pain in the CNS of CCI rats. Glial-derived mediators such as IL1β, TNFα, ROS and ATP (also acting on purinergic P2X receptors on neurons and microglia), further sustain neuroinflammation, excitotoxic stimulation and neuronal suffering [102–104].

Concluding remarks

Neuropathic pain still represents an open challenge for researchers in the field. Current therapeutic options showed limited efficacy that overall are not able to reduce or alleviate neuropathic pain in patients. Advances in understanding the molecular and cellular changes in the transition from acute to chronic pain are supporting the hypothesis of a crucial role of voltage-sensitive ion channels and intercellular/cell-to-extracellular environment channels, such as GJs and HCs. Certainly, several factors contribute to the establishment of an excitotoxic spinal environment, including overstimulation and neuronal suffering. Modulation of ion channel pool induces sensitization and hyperexcitability of sensory neurons, increasing neurotransmission and excitotoxic signals. Such a phenomenon is fostered by reactive glial cell population. Indeed, astroglial GJs and HCs severely impact extracellular compartment composition in terms of ions, small metabolites, reactive oxygen species, cytokines and messengers. This condition increases nervous system network complexity during neuropathy chronicization, characterized by a strong modulation induced by glial cell populations, considerably involved in neuronal transmission and its regulation. Thus, therapeutic approaches aiming at reducing and/or modulating CNS channels function and gating may represent successful strategies to reduce excitotoxic stimuli and microenvironment conditioning, ultimately counteracting chronicization and supporting neuroprotection.

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