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Glial Cells and Chronic Pain

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Abstract

Over the past few years, the control of pain exerted by glial cells has emerged as a promising target against pathological pain. Indeed, changes in glial phenotypes have been reported throughout the entire nociceptive pathway, from peripheral nerves to higher integrative brain regions and pharmacological inhibition of such glial reactions reduces the manifestation of pain in animal models. This complex interplay between glia and neurons relies on various mechanisms depending both on glial cell types considered (astrocytes, microglia, satellite cells or Schwann cells), the anatomical location of the regulatory process (peripheral nerve, spinal cord or brain) and the nature of the chronic pain paradigm. Intracellularly, recent advances have pointed out to the activation of specific cascades, such as mitogen associated protein kinases (MAPK) in the underlying processes behind glial activation. In addition, given the large number of functions accomplished by glial cells, various mechanisms might sensitize nociceptive neurons including a release of pronociceptive cytokines and neurotrophins or changes in neurotransmitter scavenging capacity. The authors review the conceptual advances made in the recent years about the implication of central and peripheral glia in animal models of chronic pain and discuss the possibility to translate it into human therapies in the future.

Keywords

Glia; Astrocytes, Microglia; Pain

Chronic pain is a major health issue that represents a considerable social and economic burden worldwide. Although acute nociceptive pain (coming from the activation of noxious stimuli-sensitive neurons, also called nociceptive neurons) is evolutionary advantageous to detect challenges to tissue integrity and preventing further damages, chronic pain usually shows no obvious benefit. Indeed, it may last in the absence of identifiable injury or persist long after the healing time. Symptomatically, chronic pain is also distinguished from acute pain due to the common persistence of cardinal features such as hyperalgesia (both increased response to noxious stimuli, and allodynia which is a pain response to non noxious stimuli) and spontaneous pain. Unfortunately, clinical approaches to provide chronic pain relief are hampered by a plethora of possible triggering causes, localizations and symptomatic manifestations. For instance, pain origins may be as diverse as direct damage to the nervous

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system (neuropathic pain), tumor progression (cancer pain), peripheral inflammatory insults (inflammatory pain) and from yet unclear origins (dysfunctional pain, e.g. fibromyalgia and functional bowel disorders). Current medications encompass non steroidal anti-inflammatory, steroidal, opiates, antidepressants, anticonvulsants drugs and interventional pain therapy, depending on the nature and the magnitude of pain as well. Nevertheless, these treatments usually give unsatisfactory and inconstant results as well as myriads of side effects, underscoring our need for novel molecular targets.

Interestingly, over the past two decades, a surge of attention has developed about the involvement of non neuronal glial cells, mainly astrocytes and microglia, in chronic pain. Various aspects of spinal glia nociceptive contribution have been fleshed out, to an extent that they appear now as reasonable future cell targets (Milligan and others 2009; Scholz and others 2007; Suter and others 2007; Tsuda and others 2005). The long lasting changes occurring in glia include structural alterations, cell proliferation, loss of neurotransmitter or ion buffering capacities, release of proinflammatory or proalgesic mediators and neurotoxicity. Strikingly, many models of chronic pain investigated so far result in such glial phenotypic changes, chiefly in the spinal cord (the first synaptic relay of the nociceptive pathway), but also in upper brain structures (Hains and others 2006) and in the peripheral nervous system as well (Ohtori and others 2004; Peters and others 2007b). This suggests that glial alteration could be a unifying mechanism accounting for the persistence of hypersensitivity. Furthermore, the involvement of glia in chronic pain has been strongly emphasized by the prevention and reversal of histological and behavioral manifestations of pain following treatments with molecules bearing glia-inhibitory properties (minocycline, fluorocitrate, propentophylline or alpha-aminoadipate) (Raghavendra and others 2003; Zhuang and others 2006).

We will herein review the available data regarding the involvement of glia in chronic pain, highlighting both the important conceptual breakthroughs reached and the clinical challenges still to come in order to make glial cells realistic targets for pain relief in humans.

The phenotype of spinal cord glia is altered in chronic pain

Glia represents, by far, the most abundant cells in the nervous system, largely outnumbering neurons. Two types of glial cells, namely astrocytes and microglia, have been shown to undergo structural and functional modifications in the spinal cord in models of chronic pain (Ji and others 2006; Milligan and others 2009; Tsuda and others 2005).

Astrocytes

Astrocytes represent a highly heterogeneous cell population; hence their usual definition remains vague, yet, a large part of grey matter astrocytes can be identified by the expression of specific markers such as glial fibrilary acidic protein (GFAP) or s-100_ (Kimelberg 2004). The multiplicity of astrocytic processes whose endfeet virtually enveloping every synapse together with the close apposition between astrocytic and neuronal plasma membranes renders these cells pivotal actors for the modulation of neurophysiology (Haydon 2001). The complete description of astrocytic functions is well beyond the scope of this review; however it is worth mentioning that they regulate almost all aspects of neuronal functioning. This sphere of influence includes extracellular ion homeostasis, neurotransmitter reuptake and release, control of synaptic strength, control of the blood-brain-barrier, physical compliance and metabolic control. It is classically considered that under their *resting* state, astrocytes exert this constant housekeeping function and express *basal* levels of the specific markers mentioned above (Figure 1). In opposition, upon various external stimulations, a switch in astrocytic phenotype is observed toward a so-called *state of activation* resulting in morphologically *reactive* astrocytes. This activation is

characterized by an increase in GFAP expression, an apparent enlargement of astrocytic processes, a reduction in glutamate reuptake and a release of various neuromodulatory molecules.

In 1991, Garrison and colleagues described an increased astrocytic activation in the spinal cord of neuropathic rats submitted to chronic constriction injury (Garrison and others 1991). This increase was restricted to the hemi-spinal cord ipsilateral to the lesion and the magnitude in GFAP expression mirrored the paw hypersensitivity. This indicated that a correlation exists between the persistence of pain and a fostered astrocytic activation. Since this first demonstration of a pain-related astrocytic response, many studies have reported comparable results. Firstly, extending this seminal work, spinal GFAP (as well as other astrocytic proteins such as s100_) was shown to be upregulated in all models of traumatic neuropathic pain investigated so far, including chronic constriction injury, nerve ligation, spared nerve injury and trigeminal nerve injury (all consisting in chronic pain induced by peripheral nerve ligature or cut) (Coyle 1998; Honore and others 2000; Stuesse and others 2001; Vega-Avelaira and others 2007). Despite some discrepancies between results obtained in distinct neuropathic models (Colburn and others 1999), a comparable core astrocytic reaction is described after several days in the spinal half ipsilateral to the peripheral injury (Figure 1). Likewise, various models using peripheral inflammation also show an activation of spinal astrocytes. For instance, spinal astroglial activation has been reported following peripheral formalin, zymozan or carrageenan injection as well as following colonic inflammation consecutive to intestinal administration of Trinitrobenzenesulfonic acid (Sun and others 2005; Sweitzer and others 1999). Moreover, painful peripheral tumor progression was also reported to induce an increase in GFAP-expressing astrocytes in the spinal cord (Zhang and others 2005). Furthermore, other conditions known to correlate with chronic pain in human produce astrocytic reaction in animal models, such as chemotherapy or morphine tolerance (Holdridge and others 2007; Peters and others 2007b; Song and others 2001). Together, these results suggest that a wide variety of harmful damages trigger astrocyte activation in the spinal cord that parallels the behavioral manifestation of pain.

Microglia

Microglia are resident macrophage-related cells in the central nervous system that generate innate immune responses. Similarly to what is described in astrocytes, *resting* and *activated* microglia have been defined. Resting microglial cells extend ramified processes in the parenchyma and express immunoreceptors, thus performing a constant immune surveillance (Figure 1). Upon activation (including trauma or pathogen detection), cellular changes consist in a reduction in the degree of ramifications, a release of pro-inflammatory factors and an enhanced expression of specific proteins such as complement receptors or major histocompatibility complex (MHC) proteins. Along with astrocytic changes, such modifications in spinal microglial profile have been reported in chronic pain models (Beggs and others 2007; Chang and others 2009; Ji and others 2007; Tsuda and others 2005) (Figure 2); notably, although astrocytic reaction seems to start after several days post-injury and be long-lasting, microglial activation seems to frequently occur transiently during the early phase and may even precedes astrogliosis (Hald and others 2009;Tanga and others 2004). Therefore, it is plausible that microglial reaction trigger astrocytic activation in the context of chronic pain, an hypothesis supported by the fact that reactive microglia-derived factors may activate astrocytes *in vitro* (Rohl and others 2007). It is important to notice, however, that microglial activation can also be long lasting in some models such as models neuropathy or focal burn injury (Chang and others 2009). Noteworthy, minocycline (a microglial inhibitor) prevents but not reverses long-lasting pain as opposed to fluorocitrate (an astrocytic oriented inhibitor) (Ledeboer and others 2005;Raghavendra and others 2003). This suggests that microglia may be transitorily involved in the initiation of central

modification leading to chronic pain, while astrocytic activation may be responsible for its long-lasting maintenance. The idea of a very upstream influence of microglia in the development of chronic pain is further supported by evidence showing that intrathecal injection of *in-vitro* activated microglia triggers thermal hyperalgesia and tactile allodynia whereas astrocytes did not (Narita and others 2006b;Tsuda and others 2003). Nevertheless, the exact nature of microglial mediators activating astrocytes and downstream nociceptive pathways remains to be determined.

Intracellular cascades during glial activation

The intracellular events occurring in glial cells upstream to these modifications are incompletely understood. Nevertheless, some important breakthroughs have been made in the last few years. In particular, mitogen-activated protein kinases (MAPKs) have emerged as important glial intracellular mediators (Ji and others 2009; Ji and others 2007). MAPKs are subclassified into three main types of kinases families involved in as many distinct pathways, namely extracellular signal-regulated kinases (ERK), p38 and c-jun N-terminal kinases (JNK). Activations of individual MAPKs in the spinal cord following pain-generating peripheral injury occur in a cell-specific and model-specific manner. Indeed, in neuropathic pain paradigms and focal burn injury, the p38 pathway is activated in microglia (Chang and others 2009; Jin and others 2003; Tsuda and others 2004) (Figure 3) and the JNK cascade in astrocytes (Ma and others 2002; Zhuang and others 2006). Conversely, it has been reported that morphine tolerance is correlated to microglial p-38 activation but ERK activation in astrocytes (Wang and others 2009). Importantly, intrathecal blockade of these pathways have been successfully utilized to prevent and reverse behavioral manifestations of chronic pain in various models (Jin and others 2003; Tsuda and others 2004; Wang and others 2009; Wen and others 2009; Zhuang and others 2006). In particular, the inhibition of astrocyte-related JNK activation in the spinal cord of neuropathic rats with a JNK inhibitor peptide (D-JNKI-1) was able to prevent and reverse the occurring of allodynia, suggesting a key role played by astrocytic JNK in the development of neuropathic pain (Zhuang and others 2006). Together, this suggests that spinal glial MAPKs may represent future pharmacological targets against pain, and underscores our need to better understand the cell and model specificity of MAPKs activation in pain.

Glia-activating mechanisms and pro-nociceptive glial actions in chronic pain

The molecular events triggering astrocytic and microglial activation as well as the signals resulting from this activation producing pain hypersensitivity remain largely unclear. An increasing number of studies have recently addressed this question and several mechanisms seem to be consistently involved (Figure 4). First, the extracellular activating events, especially in neuropathic pain arising from peripheral damage, are very likely originating from sensory neuronal terminals reaching the spinal cord since blockade of nerve conduction following nerve injury with local anesthetics prevents the activation of p38-MAPK in spinal microglia (Suter and others 2009;Wen and others 2007). Interestingly, blockade of non nociceptive A-β fibers but not blockade of nociceptive C or A-δ fibers inhibits microglial activation (Figure 5), suggesting that the activity of thick myelinated fibers is essential for microglial activation (Suter and others 2009). As astrocytes and microglia express a large repertoire of receptors for neurotransmitters (D'Antoni and others 2008;Derocq and others 1996;Masmoudi-Kouki and others 2006;Masmoudi and others 2005;Patte and others 1999; Verkhratsky and others 2007), a sustained release of neurotransmitters, ATP and neuropeptides (such as Substance P) might be partially accountable for spinal glial changes. Furthermore, other candidate molecules, such as chemokines (a portemanteau word from chemotactic cytokines) have been recently pointed

out as neuron-to-glia mediators (Gosselin and others 2008). In particular, several specific members of the chemokine family have been detected in sensory neurons, but the membrane-anchored and cleavable chemokine fractalkine/CX3CL1 expressed by neurons has raised a special interest in neuro-glial communication as its receptor CX3CR1 is mainly found on microglial cells and intrathecal blockade of either ligand or receptor reduce pain in neuropathic or inflammatory pain models (Clark and others 2009;Milligan and others 2004;Sun and others 2007;Verge and others 2004;Zhuang and others 2007).

Matrix metalloproteases (MMPs), and in particular MMP9 and MMP2, are also implicated as mediators for the response following inflammation or nerve damage response. MMP2 is increase in the DRG neurons, and MMP9 into satellite cells after peripheral nerve damage and contribute to the cleavage of the cytokine interleukin-1_ into its active form. The early and transient increase of MMP9 mediates the activation of microglia and was correlated with the development of neuropathic pain in experimental pain models (Kawasaki and others 2008).

As a result of their activation, due to their immune properties, microglia and astrocytes may sensitize the nociceptive pathway in part through the release of proinflammatory factors such as cytokines, prostaglandins or neurotrophins (McMahon and others 2005). In particular, the chemokine CCL2/MCP-1 has recently emerged as a putatively important astrocyte-derived pronociceptive factor, which amplifies excitatory glutamatergic currents (Gao and others 2009). Furthermore, another important pronociceptive action of CCL2 may rely on its potent attenuating effect on inhibitory GABA-ergic currents in spinal neurons (Gosselin and others 2005). Besides, neurotrophins released by glial cells also act as neuron sensitizing factors in the spinal cord. In particular, brain derived neurotrophic factor (BDNF) has been regularly put forward as a key microglial mediator in models of chronic pain (Li and others 2008; Lu and others 2009), an action at least partly due to the reduction in the expression of the potassium–chloride exporter KCC2 and the ability to reverse the polarity of GABA-induced currents in spinal neurons leading to excitatory currents (Coull and others 2005). Beyond immunity, given the wide spectrum of functions fulfilled by astrocytes, alterations in practically any aspect of their physiology may result in a perturbed nociceptive neurotransmission. For instance, various models of chronic pain have been associated with an alteration in spinal astrocytic capacity to buffer glutamate or GABA resulting in the reinforcement of nociceptive neurotransmission (Daemen and others 2008; Ng and others 2001; Sung and others 2003). This is of particular importance as pharmacological modulation of spinal glial glutamate and GABA reuptake are sufficient to modify nociception and pain behaviors (Hu and others 2003; Liaw and others 2005).

Pain-related glial activation in the peripheral nervous system and in the brain

Other glial cells: Satellite cells, Schwann cells

Beyond the involvement of central microglia and astrocytes in chronic pain, mounting evidence also argue in favor of a peripheral glial pronociceptive contribution. First, Schwann cells forming both myelin sheets (around non nociceptive A_ fibers and nociceptive A_ fibers) and non myelinating Remak bundles (around nociceptive C fibers) have been shown to react to peripheral insults. One first consequence of Schwann cell activation may be a possible modification of myelin properties resulting in altered conduction properties of nociceptive fibers. In accordance with this, a pronociceptive degradation of myelin protein via Schwann cell protease synthesis has been described following nerve damage (Kobayashi and others 2008). Second, this release of proteases from Schwann cells may trigger a disruption of the blood-nerve-barrier allowing circulating

immune cells to infiltrate the nerve and exert nociception-facilitating actions (Scholz and others 2007).

Satellite glial cells (SGC) represent another strategically positioned cell group for nociception modulation as they entirely surround sensory neurons within spinal or trigeminal ganglia (Ohara and others 2009). Although SGC functions are largely unknown, they present numerous similarities with astrocytes, by sensing neighboring neuronal activity and are thought to exert regulatory functions (Hanani 2005). Interestingly, a strong increase in GFAP expression in SGC has been described in various pain models, including peripheral tissue injury, nerve damage, or systemic chemotherapy-induced hyperalgesia (Chudler and others 1997; Peters and others 2007a; Stephenson and others 1995). The mechanisms by which satellite cells sensitize sensory neurons are incompletely resolved. Nevertheless, an increased level of gap-junction-based communication has been described following peripheral injection of CFA, painful colonic obstruction or nerve lesion underscoring a possible role of direct cell-to-cell coupling (Dublin and others 2007; Huang and others 2005). In addition, following nerve injury, SGC upregulate the synthesis of neurotrophins acting both as promoters of sympathetic sprouting within the ganglion (a mechanism suspected to foster sensory neuron activity) (Pertin and others 2007) and as direct sensitizers of nociceptive neurons (Zhou and others 1999; Zhou and others 2000). Finally, consecutively to nerve or tissue damage, an increased expression of cytokines is observed in the DRG advocating in favor of a sensitizating influence of SGC-released inflammatory molecules on sensory neurons. Especially, it has been recurrently pointed that tumor necrosis factor (TNF)-_ is upregulated in DRG satellite cells in parallel to TNF-receptor in DRG sensory neurons, suggesting an important role of TNF in peripheral sensitization (Miyagi and others 2006; Ohtori and others 2004). Furthermore, it has been shown that persistent up-regulation of matrix metalloprotease-2 (MMP-2) in satellite cells contributes to the maintenance of neuropathic pain by active cleavage of IL-1b and the late phase of activation of astrocytes (Kawasaki and others 2008).

Glial changes in the brain

Beyond the glial changes taking place in the spinal cord and in the peripheral nerves, marked modifications also occur in various brain regions. These include thalamic microglial activation to nociceptive spinal cord injury (Hains and others 2006; Zhao and others 2007), astrocytic activation in the cingulate cortex following sciatic nerve ligation (Kuzumaki and others 2007; Narita and others 2006a) and in the nucleus of the tractus solitari following colonic inflammation (Sun and others 2005). Importantly, the glial reaction observed in regions not directly involved in nociception but rather in limbic circuitry (such as the prefrontal cortex) suggest that glia may be involved in the regulation of the affective component of pain. In support of this hypothesis, an increasing corpus of data report that perturbation of astrocytic physiology in corticolimbic brain areas may be involved in mood and affective disorders such as major depression (Rajkowska and others 2007).

Is glial activation a general hallmark of chronic pain?

As we discussed above, the vast majority of chronic pain models investigated so far have shown some degree of glial activation. Nevertheless, the tempting idea of a universal association between chronic pain and glia should be taken with caution. First, to date, many models of persistent pain have only been scarcely (or even simply not) investigated with regard to their possible association with glial changes, including models of visceral pain, interstitial cystitis, fibromyalgia, migraine, post-herpetic or alcoholic neuralgia and phantom limb pain. It is therefore possible that some of these paradigms do not bear glial reaction. In accordance with this, it has been claimed that experimental muscle pain induced by repeated intramuscular acetic acid was not mediated by glial cells showing that some chronic pain

might arise in the absence of detectable glial reaction (Ledeboer and others 2006). In addition, discrepancies have emerged regarding the glial reaction consecutive to peripheral inflammation, especially following injections of CFA. Indeed, many studies have reported an absence of glial reaction following peripheral pro-nociceptive CFA inflammation (Clark and others 2007; Honore and others 2000; Lin and others 2007), suggesting that, in such cases, glial reaction is unlikely to account for pain.

It is worth mentioning that the analysis of glial changes have been often restricted to modifications in canonical markers expression (for instance GFAP, s-100_, cd-11b/ox-42), the synthesis of proinflammatory mediators (for example cytokines or prostaglandins) or the possibility to reverse hyprealgesia by using glial inhibitors. However, it is important to consider that glial changes might occur at a subtle scale than the gross glial alterations usually sought in chronic pain, resulting in alterations such as moderate (yet biologically significant) perturbations in neurotransmitter reuptake, ion homeostasis or energy supply.

Is there a pain-related glial reaction in humans?

The demonstration that animal models of chronic pain present a marked pronociceptive glial reaction in both peripheral and central nervous system represents a significant advance in our understanding of the persistence of pain. However, there is still a knowledge gap to be filled between these data and the possible involvement of glial activation in human since very limited data are available in patients. The task aiming at extending animal results to acceptable treatments in human disease is therefore twofold.

First, only scarce studies have investigated glial change in human chronic pain, hence the unequivocal demonstration that glial activation occurs in hypersensitized patients remains to be provided. Nevertheless, in a postmortem study, a glial reaction (both astrocytic and microglial) has been reported in the spinal cord of one patient with a chronic regional pain syndrome, a condition associating with sharp pain and autonomic abnormalities (Del Valle and others 2009). In addition, an increase in the concentration of the glial marker s-100_ was reported in the cerebrospinal fluid of patients with lumbar disc herniation and in the serum of children with recurrent headache (Brisby and others 1999; Papandreou and others 2005). Together, these results point to a likely glial reaction associated with chronic pain in human. However, systematic studies are still lacking demonstrating a correlation between the magnitude of glial markers in the cerebrospinal fluid or in spinal tissue and the intensity of pain in patients.

In addition, one major issue in therapeutics will consist in the development of specific glial inhibitors able to reverse (and not only prevent) phenotypic changes in glia as in many cases, pharmacological interference in chronic pain often arise long after the initiation of glial plasticity. The specificity of glial inhibitors will surely improve together with a better understanding of the mechanisms behind the changes of phenotype in glial cells. So far, glial inhibitors utilized in pain models are either used for their anti-inflammatory properties (propentophylline, pentoxyfylline, metothrexate, minocycline) based upon the idea that gliosis is pro-nociceptive due to a release of pro-inflammatory mediators, or metabolic toxicity (fluorocitrate, fluoroacetate) due to their apparent selectivity in inhibiting glial metabolism. However; 1) it is likely not advantageous to fully attenuate glial function as astrocytes and microglia exert vital housekeeping and surveillance functions; 2) the action of these drugs is usually not restricted to one cell population; 3) as glia inhibition is actually an epiphenomenon among the wide spectrum of their biological actions, these drugs are predicted to present a constellation of side effects in humans, especially if used systemically; 4) some of these molecules present a high risk of either acute or cumulative toxicity which could hamper their chronic use; 5) the efficacy of some of these drugs as pain inhibitors in

several animal models is still debated (Shumilla and others 2005). Consequently, the development of selective glial inhibitors targeting one cell type and possibly one molecular pathway will be required prior to considering glia as putative targets for pain relief.

Conclusions

Mounting evidence gathered from animal studies champion the hypothesis that glial cells respond to many insults by enhancing hypersensitivity in chronic pain. Many molecular events in glia have been put forward as new strategies for pain-killer drug development, including purine and chemokine-driven glial activation, intracellular activation of specific MAPKs cascades, glial-release of cytokine and neurotrophin or astrocytic neurotransmitter scavenging capacity. Nevertheless, a more detailed description of reported discrepancies between pain models as well as further investigations in less-investigated pain models are required for a better understanding of glial involvement in chronic pain. Additionally, reliable human data are still needed to ascertain that such glial reactions occur in human and that glial-oriented therapeutics may be foreseen in a near future.

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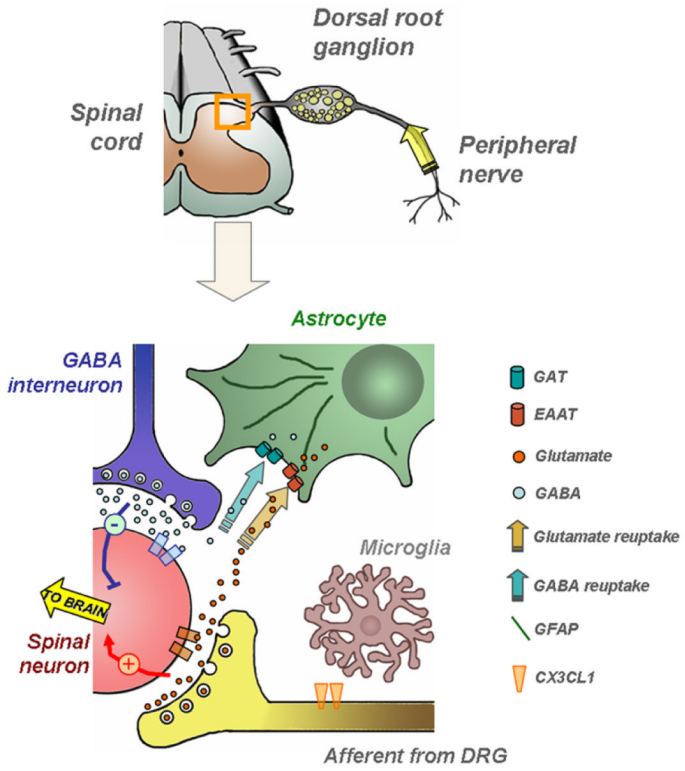

Figure 1.
Schematic representation of glial events occurring in normal nociceptive state: under basal condition, acute pain signaling is likely not influenced by microglial cells in a resting stage. Conversely, astrocytes are actively involved in neuronal physiology, particularly the reuptake of glutamate and GABA. This continuous glutamate and GABA reuptake by astrocytic processes around synapses between sensory afferents and inhibitory interneurons respectively allows a fast and regulated nociceptive neurotransmission toward upper brain regions.

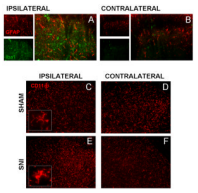

Figure 2.

Photomicrographs illustrating the glial reaction in the ipsilateral rat spinal cord and its various aspects 7 days after peripheral nerve injury (spared nerve injury model, SNI). A-B, double immunofluorescence labeling showing that both astrocytic marker GFAP (red) and microglial protein Iba-1 (green) are upregulated in the ipsilateral dorsal horn (A) in comparison to the contralateral side (B). Microglial reaction may also be visualized by labeling the integrin CD11-b (C-F). In neuropathic animals (E-F), an increase in CD11b immunoreacivity is observed ipsilaterally to the lesion site (E) in comparison to contralateral side (F) and spinal cord from sham-operated animals (C-D). Inserts in C and E show high magnification images of CD11-b labeled microglia from sham or neuropathic rats respectively. Note the change in cell shape in neuropathic animals, from ramified to activated form. Images are from personal unpublished data library.

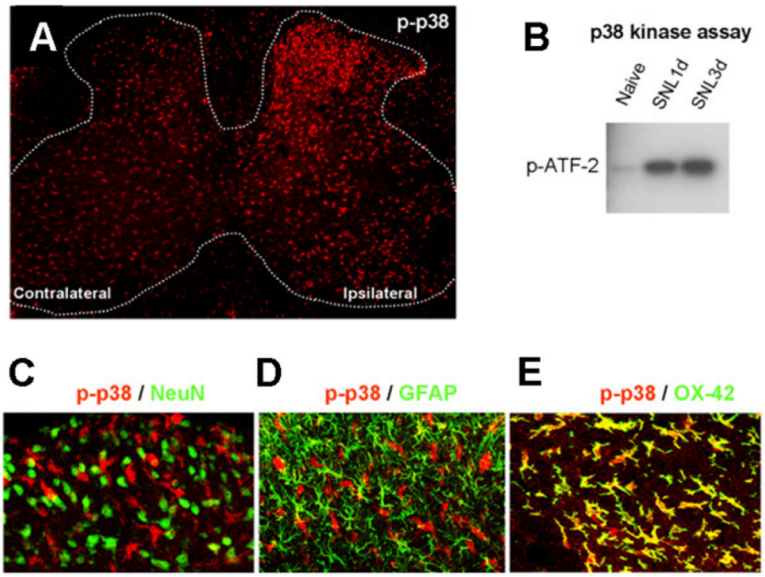

Figure 3.

Activation of p38 MAPK in the spinal cord subsequently to nerve injury in the Spinal Nerve Ligation (SNL) model of neuropathic pain. A, immunofluorescence labeling showing an increase level of phosphorylated p38 in the spinal cord ipsilaterally to the lesion site, 3 days post-surgery. B, kinase assay showing a fostered activity of p38-MAPK in neuropathy. An elevated capacity of p38 SNL spinal extracts to phosphorylate its substrate ATF-2 in comparison to naive extracts is obvious one day and 3 days post surgery. C-E, dual immunofluorescence showing that phosphorylated p38-MAPK does not colocalize with neuronal marker NeuN (C), astrocytic protein GFAP (D) but instead is present in microglia as assessed by the overlapping signal using the OX-42 antibody, detecting microglial CD11-b (E). Adapted from (Ji and others 2007).

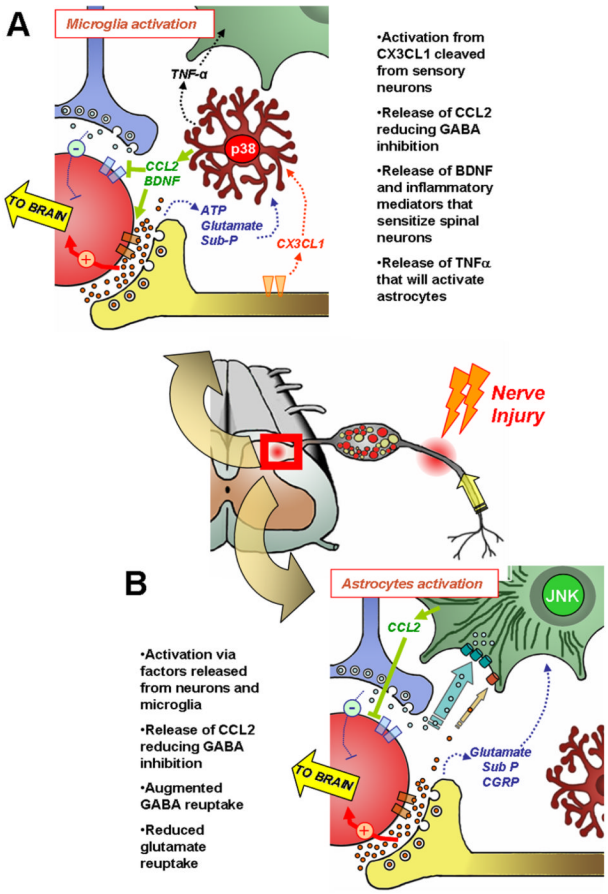

Figure 4.

Schematic illustartion of microglial (A) and astrocytic (B) events taking place in the spinal cord in neuropathic pain. A: In chronic neuropathic pain, under the influence of neuronal factors (such as CX3CL1, ATP or neuromediators), microglia undergoes changes in phenotype including an activation of p38 MAPK pathway. So-called activated microglia releases factors (such as cytokines) that in turn reinforce nociception by reducing the potency of GABAergic inhibition, sensitizing spinal neurons and activating astrocytes. B: An astrocytic activation also occurs (characterized by an activation of the intracellular JNK pathway) consequently to both neuronal releases of high amounts of neuromediators and microglial production of cytokines such as TNF-α. As a result of astrocyte reaction, a reduction of glutamate scavenging capacity together with an increase in GABA uptake reinforces pain signaling as well. Furthermore, reactive astrocyte release cytokines such as CCL2, participating in the loss of the GABAergic inhibition.

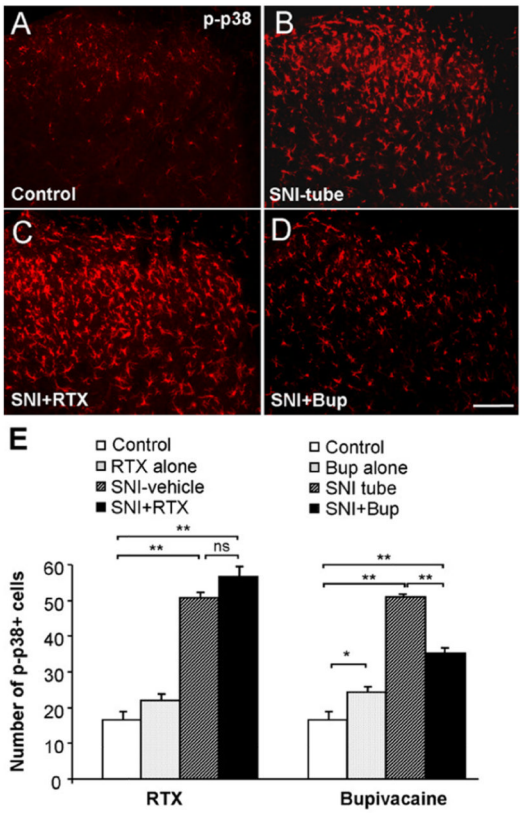

Figure 5.

Nerve block inhibiting the activity of large Aβ fibers reduces the activation of p38 MAPK in spinal microglia in the rat spared nerve injury (SNI) model of neuropatic pain. A-D, immunofluorescence micrographs depicting the effects of nerve blocks on spinal p38 phosphorylation following surgery. An increase in p38 phosphorylation is obvious following SNI (B) in comparison to control spinal cord (A). Blocking nociceptive C and Aδ fibers conduction using pre-surgical Resiniferatoxin (RTX) is ineffective in reducing microglial p38 phosphorylation (C) whereas non-nociceptive (Aβ fibers) nerve block with Bupivacain (Bup) results in a striking inhibition of p38 activation (D). The bar histogram shown in E shows the corresponding cell count quantifications. Complementary methodological informations and discussion details may be found in the related article (Suter and others 2009).