Neurosci Bull April 1, 2012, 28(2): 111−120. http://www.neurosci.cn
DOI: 10.1007/s12264-012-1204-z

·Review·

AMPA receptor trafficking in inflammation-induced dorsal horn central sensitization

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Abstract: Activity-dependent postsynaptic receptor trafficking is critical for long-term synaptic plasticity in the brain, but it is unclear whether this mechanism actually mediates the spinal cord dorsal horn central sensitization (a specific form of synaptic plasticity) that is associated with persistent pain. Recent studies have shown that peripheral inflammation drives changes in α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR) subunit trafficking in the dorsal horn and that such changes contribute to the hypersensitivity that underlies persistent pain. Here, we review current evidence to illustrate how spinal cord AMPARs participate in the dorsal horn central sensitization associated with persistent pain. Understanding these mechanisms may allow the development of novel therapeutic strategies for treating persistent pain.

Keywords: dorsal horn; GluA1; GluA2; inflammation; persistent pain; receptor trafficking

1 Introduction

Persistent or chronic pain arising from inflammation and tissue or nerve injury is one of the most common syndromes seen clinically. Despite intensive research into the neurobiologic mechanisms of persistent pain during the past decades, it is still poorly managed by current drugs such as opioids and nonsteroidal anti-inflammatory drugs[1]. Persistent pain is characterized by spontaneous or intermittent burning pain, an exaggerated response to painful stimuli (hyperalgesia), and pain in response to normally innocuous stimuli (allodynia). It is believed that a specific form of synaptic plasticity known as central sensitization underlies the mechanisms by which persistent pain develops and is maintained. Understanding such mechanisms will allow the development of novel therapeutic strategies to treat persistent pain.

The α-amino-3-hydroxy-5-methyl-4-isoxazolepro pionic acid (AMPA) receptor (AMPAR) is a glutamate ionotropic receptor that is integral to fast excitatory synaptic transmission and plasticity at synapses in the central nervous system[2,3]. In addition to mediating the acute spinal processing of nociceptive and non-nociceptive inputs, AMPARs in the dorsal horn may also participate in central sensitization under persistent pain conditions[4]. Multiple intrathecal treatment with the non-selective AMPAR antagonist CNQX beginning 15 min prior to nerve ligation significantly (but not completely) reduces the development of nerve injury-induced thermal hyperalgesia, and this effect persists for up to 10 days[5]. Interestingly, single intrathecal post-treatment with selective or nonselective AMPAR antagonists partially and temporarily attenuates thermal hyperalgesia and mechanical allodynia after peripheral nerve injury[5,6]. Inhibition of spinal Ca^{2+}-permeable AMPAR blocks thermal

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Article ID: 1673-7067(2012)02-0111-10
Received date: 2012-01-06; Accepted date: 2012-01-27

injury-induced mechanical allodynia and carrageenan-induced thermal hyperalgesia and mechanical allodynia[7,8]. Furthermore, intrathecal administration of selective AMPAR antagonists attenuates complete Freund's adjuvant (CFA)-induced mechanical and thermal pain hypersensitivity during both the development and maintenance of persistent pain at doses that do not affect locomotor function or responsiveness to acute pain[9]. Electrophysiologic studies revealed that AMPAR blockade reduces the receptive field areas of superficial dorsal horn neurons[10,11]. Using mice that lack GluA1, GluA2, or GluA3, Hartmann *et al*.[12] demonstrated that AMPARs are critical determinants of spinal cord nociceptive plasticity and inflammatory pain. The evidence suggests that dorsal horn AMPARs may be critical for the central sensitization associated with persistent pain. However, how spinal AMPARs participate in central sensitization under persistent pain conditions is still incompletely understood.

Recent studies have indicated that peripheral inflammatory insults drive changes in AMPAR subunit trafficking via N-methyl-*D*-aspartic acid (NMDA) receptor-triggered activation of protein kinases in the dorsal horn and that these changes contribute to central sensitization in the development and maintenance of persistent inflammatory pain[4]. Here I review the current evidence regarding changes in AMPAR subunit trafficking in dorsal horn neurons after peripheral inflammation and tissue or nerve injury and discuss potential mechanisms by which such changes participate in the development and maintenance of persistent pain.

2 AMPAR channel structure and expression in spinal cord

AMPARs are composed of four subunits, GluA1 to GluA4 (or GluR1 to GluR4). Each subunit comprises an N-terminal extracellular amino domain, a ligand-binding domain, a receptor-channel domain, and an intracellular C-terminal domain[3]. It should be emphasized that the receptor-channel domain consists of three transmembrane segments (M1, M3, and M4) and one re-entrant loop within the membrane (M2). Because the M2 loop forms part of the channel pore, it controls the flow of ions (e.g. Ca^{2+}) through the AMPAR channel[13,14]. In addition, the C-terminal intracellular domain presents multiple protein phosphorylation sites for various known protein kinases such as protein kinase A (PKA), protein kinase C (PKC), and Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII), and several binding motifs for various membrane-related and intracellular proteins, e.g. the scaffolding proteins[13,14]. Functional AMPARs are homomeric or heteromeric tetramers of GluR subunits. In the adult mammalian central nervous system, GluA1 and GluA2 subunits are ubiquitously expressed and present in most AMPARs. Whereas GluA1, GluA3, and GluA4 convey high Ca^{2+} permeability to AMPAR channels, GluA2 imparts low Ca^{2+} permeability because it carries an arginine residue in its pore-forming M2 segment (inserted by Q/R site RNA editing during development)[3].

Morphological studies indicate that all four GluR subunits are found within the dorsal horn of the spinal cord[15-17]. GluA1 is highly expressed in the superficial dorsal horn (laminae I–II) but exhibits low expression in the deeper dorsal horn[4]. GluA2 expression has been observed throughout the dorsal horn, but it is distributed predominately in inner lamina II[4]. GluA3 is weakly expressed in the deep laminae. GluA4 was recently detected in large NK1 receptor-expressing projection neurons in lamina I[18]. Under electron microscopy, most GluA1 and GluA2 immunoreactive products are restricted to the postsynaptic density, with little reactivity in axons and terminals in the superficial dorsal horn[4]. Thus, GluA1 and GluA2 are the two key subunits that comprise the AMPAR channel in the dorsal horn.

3 Trafficking and functional changes of dorsal horn AMPARs after peripheral noxious stimuli

Unlike the NMDA receptor, the AMPAR is not stable at synapses; its expression is dependent on a balance between two dynamic processes. In one, AMPAR subunits rapidly and constitutively cycle between intracellular stores and the cellular membrane surface. In the second, AMPAR subunits exchange between the extrasynaptic and

synaptic membranes by lateral diffusion. Any factors that disturb these processes can change the synaptic expression of AMPAR subunits and further affect AMPAR synaptic strength.

Recent studies have demonstrated that peripheral noxious insults upset the flux of AMPAR subunits and alter their synaptic and extrasynaptic trafficking in dorsal horn neurons. One study showed that painful visceral stimulation produced by capsaicin injection into the colon rapidly and significantly increases the level of membrane GluA1 protein and correspondingly reduces the amount of cytosolic GluA1, without changing total GluA1 or GluA2 protein levels in the dorsal horn[19] (Table 1). Another study demonstrated that capsaicin injection into rat hind-paw increases the density of GluA1-containing AMPARs and the ratio of GluA1 to GluA2/3 in postsynaptic membrane in the superficial dorsal horn[20]. In addition, pain hypersensitivity evoked by intraplantar carrageenan and pain behaviors induced by intraplantar formalin are associated with the movement of GluA1, but not GluA2, into neuronal membrane in the dorsal horn[21,22] (Table 1). Interestingly, intraplantar injection of CFA into a hind-paw produces changes in the subcellular distribution of both GluA1 and GluA2 proteins in dorsal horn neurons, although it does not alter the total expression of GluA1 and GluA2 proteins[9,23] (Table 1). The level of cytosolic GluA2 is markedly increased, and the level of membrane-bound GluA2 is significantly decreased in the dorsal horn 1 and 3 days after CFA injection[9,23]. Conversely, the amount of GluA1 is significantly reduced in cytosol and increased in the neuronal membrane 1 day after CFA injection[9]. Furthermore, researchers found decreased synaptic GluA2 and increased extrasynaptic GluA1 in the superficial dorsal horn 1 day after CFA injection[23-25]. In contrast, peripheral incision and nerve injury failed to alter the expression and localization of GluA1 or GluA2 in cytosolic and plasma membrane fractions from the dorsal horn[26,27]. This evidence indicates that different peripheral nociceptive insults produce distinct changes in dorsal horn AMPAR subunit trafficking.

Table 1. Trafficking changes of GluA1 and GluA2 in dorsal horn after inflammation

Model	GluA1			GluA2		
	Cytosol	Membrane	Total	Cytosol	Membrane	Total
ICo capsaicin[19]	↓	↑	–	–	–	–
IPl formalin[22]	↓/↑	↑	N/A	N/A	N/A	N/A
IPl carrageenan[21]	↓	↑	N/A	–	–	N/A
IPl CFA[9,23]	↓	↑	–	↑	↓	–

CFA, complete Freund's adjuvant; ICo, intracolonic; IPl, intraplantar; N/A, not available; "↓", decrease; "↑", increase; "↓/↑", decrease early and increase late; "–", no change.

Peripheral noxious insults also alter the properties of synaptic and extrasynaptic AMPARs in dorsal horn neurons. One key property that is altered is Ca^{2+} permeability. Selectively blocking Ca^{2+}-permeable AMPARs inhibits AMPAR-mediated evoked excitatory postsynaptic currents (eEPSCs) to a greater degree in lamina II neurons from CFA-treated animals than in those from saline-treated animals[23], indicating that CFA injection increases synaptic Ca^{2+}-permeable AMPARs in the superficial dorsal horn. Compared to saline, CFA also enhances the inward rectification of eEPSCs and significantly reduces the rectification index in lamina I projection neurons[28] and lamina II interneurons[23,24] 1 day after CFA injection. In addition, extrasynaptic AMPAR currents and Ca^{2+} permeability increase dramatically in the lamina II neurons characterized by intrinsic tonic firing properties, but not in those that exhibit strong adaptation, 1 day after CFA injection[25]. This increase is accompanied by an inward rectification of AMPA-induced currents and enhanced sensitivity to a highly selective Ca^{2+}-permeable AMPAR blocker[25]. The Ca^{2+}-permeability of AMPARs can also be visualized by kainate-induced cobalt uptake. One day after injecting one hind-paw of rats with CFA, we found that the number of cobalt-positive neurons was significantly increased in dorsal horn neurons on the side ipsilateral to the injection[25]. Taken together, these findings suggest that peripheral inflammation leads to a switch from Ca^{2+}-impermeable AMPARs to Ca^{2+}-permeable AMPARs at both the synaptic and extrasynaptic sites of dorsal horn neurons. This switch is very likely attributable to a change in AMPAR subunit

composition (that is, GluA1 membrane insertion and GluA2 internalization).

4 Molecular mechanisms that underlie inflammation-induced changes in dorsal horn AMPAR trafficking

As noted above, the C-terminal intracellular domain of AMPAR subunits contains multiple protein phosphorylation sites for various protein kinases and several binding motifs for scaffolding proteins. New research has revealed that these phosphorylation sites and binding motifs impact AMPAR subunit trafficking and function. For example, phosphorylation of GluA1 at the site of serine 845 (Ser^{845}) by PKA elevates the channel open probability and peak amplitude of the AMPAR, increases GluA1 expression in the plasma membrane, and reduces AMPAR internalization[29-31]. Phosphorylation of GluA1 at Ser^{831} by PKC/CaMKII increases the signal channel conductance of synaptic AMPARs[32]. CaMKII activation also drives GluA1-containing AMPARs to synapses by a mechanism that requires the binding of GluA1 to its scaffolding protein[33]. In addition, phosphorylation of GluA1 Ser^{818} by PKC promotes GluA1 membrane insertion and facilitates an interaction with protein 4.1N, a scaffolding protein involved in the synaptic delivery and stabilization of GluA1[34,35]. Further study showed that protein 4.1N is required for activity-dependent GluA1 insertion at extrasynaptic sites by PKC-dependent phosphorylation of GluA1 Ser^{816} and Ser^{818}. Phosphorylation at these sites enhances 4.1N binding to GluA1 and facilitates GluA1-containing AMPAR insertion into the extrasynaptic plasma membrane[36]. Thus, it is very likely that protein 4.1N and several serine phosphorylation sites of the GluA1 C-terminus participate in the regulation of synaptic and extrasynaptic GluA1 trafficking.

Peripheral inflammation alters the phosphorylation status of GluA1 serine residues. Intraplantar injection of capsaicin or CFA increases the phosphorylation of GluA1 Ser^{831} and Ser^{845} in the dorsal horn[37-39]. Our recent data demonstrated that dorsal horn PKCα knockdown blocks CFA-induced increases in the number of Ca^{2+}-permeable AMPARs and the proportion of Ca^{2+}-permeable subunits at the extrasynaptic site. From these data, it appears that the inflammation-induced increase in extrasynaptic Ca^{2+}-permeable AMPARs is due to PKC-dependent phosphorylation of GluA1 at the serine residues and subsequent insertion of GluA1-containing AMPARs into the extrasynaptic plasma membrane of dorsal horn neurons. However, this conclusion must be further confirmed by investigating whether targeted mutation of GluA1 phosphorylation sites (e.g., Ser^{831}, Ser^{845}, Ser^{816} and Ser^{818}) affects inflammation-induced increases in GluA1 membrane insertion and the number of Ca^{2+}-permeable AMPARs at extrasynaptic sites of dorsal horn neurons.

Recent evidence has revealed that spinal cord glial activation is involved in the increase of GluA1 phosphorylation and changes in GluA1 trafficking in the dorsal horn after inflammation. Choi *et al.*[21] showed that intraplantar carrageenan promoted GluA1 membrane insertion and phosphorylation of GluA1 Ser^{845} in the dorsal horn but that these increases were blocked by a tumor necrosis factor (TNF) antagonist. Thus, the increased GluA1 phosphorylation and membrane insertion may be dependent on TNF, a proinflammatory cytokine. Additional investigation is needed to determine how TNF released from spinal glia participates in the regulation of neuronal GluA1 phosphorylation and trafficking in the dorsal horn after inflammation.

Like GluA1, GluA2 contains a binding motif at its C-terminus for two scaffolding proteins: AMPAR-binding protein (ABP)/glutamate receptor-interacting protein (GRIP) and protein interacting with C kinase 1 (PICK1). ABP/GRIP functions as an anchor to stabilize GluA2 at the synaptic membrane[40-42]. PICK1 acts as a transporter to recruit PKCα to ABP/GRIP-GluA2 complexes; the kinase then phosphorylates GluA2 at Ser^{880}[43-45]. Studies from *in vitro* cell lines and neuronal culture have shown that GluA2 phosphorylation at Ser^{880} by PKCα reduces the binding of GluA2 to ABP/GRIP, but not to PICK1, and promotes GluA2 internalization[43,44,46,47].

The data from our laboratory indicate that PKC phosphorylation at GluA2 Ser^{880} is triggered by NMDA receptor activation and contributes to dorsal horn GluA2 inter-

nalization in inflammatory pain. Under normal conditions, dorsal horn NMDA receptors are inactive. GluA2 interacts with both ABP/GRIP and PICK1, but PICK1 also binds to inactive PKCα in dorsal horn neurons[23]. In cultured dorsal horn neurons, activation of NMDA receptors and PKCα markedly increases the level of GluA2 phosphorylation at Ser^{880} and decreases the surface expression of GluA2[23]. Activation of AMPARs and group 1 metabotropic glutamate receptors does not have this effect. Consistently, blockade of dorsal horn NMDA receptors and PKCα activity attenuates CFA-induced increases in GluA2 phosphorylation at Ser^{880} and cytosolic GluA2 expression in the dorsal horn[23] (Fig. 1). Furthermore, blocking the CFA-induced increase in phosphorylation of GluA2 Ser^{880} reduces CFA-evoked GluA2 internalization in dorsal horn neurons[23]. The increased intracellular Ca^{2+} concentration that results from Ca^{2+} influx through activated NMDA receptors may activate PKCα to phosphorylate GluA2 at Ser^{880}. This phosphorylation would disrupt GluA2 binding to ABP/GRIP and promote GluA2 internalization in dorsal horn neurons. Indeed, the binding affinity of GluA2 to GRIP1 is significantly reduced in dorsal horn neurons after intraplantar CFA injection[23]. Moreover, NMDA receptor-triggered GluA2 internalization requires Ca^{2+} influx directly through the NMDA receptor channel[48,49]. AMPA complexes are physically coupled to NMDA receptor complexes by a PSD-95–stargazin linkage with GluA1/2/4 and NR2A/NR2B and to PKCα by PICK1 with GluA2 in the dorsal horn[23]. This coupling may provide a molecular basis for an NMDA receptor–PKCα–AMPAR signal cascade and enable Ca^{2+} to reach PKCα through NMDA receptor channel influx. The result would be phosphorylation of both GluA1 and GluA2 and changes in trafficking of both subunits. This conclusion is supported by the evidence that both GluA1 membrane insertion and GluA2 internalization require NMDA receptor activation in central neurons[23,48-53]. Therefore, NMDA receptor/PKCα activation may be responsible for CFA-induced changes of GluA1 and GluA2 trafficking in dorsal horn neurons after inflammation.

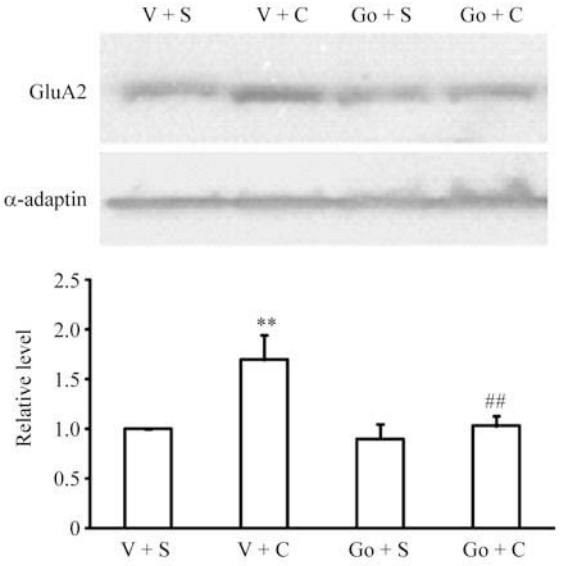

Fig. 1. Protein kinase C alpha (PKCα)-dependent GluA2 internalization in dorsal horn 1 day after complete Freund's adjuvant (CFA) injection into rat hind-paw. Two intrathecal injections of the selective PKCα inhibitor Go6976 (Go, 25 μg) given at a 12-h interval blocked the CFA-induced increase in GluA2 in the 150 k-g dorsal horn fraction 1 day post CFA injection (unpublished data). *n* = 4/group. $^{**}P$ <0.01 *vs* V + S group; $^{\#\#}P$ <0.01 *vs* V + C group. C, CFA; S, saline; V, vehicle (20% DMSO).

It should be noted that the binding motif in the GluA2 C-terminus also binds other proteins that are involved in the regulation of synaptic GluA2 trafficking. For example, GluA2 interacts with N-ethylmaleimide-sensitive fusion (NSF) protein. This protein maintains the synaptic expression of GluA2-containing AMPARs, displaces PICK1 from the PICK1-GluA2 complex, and facilitates the delivery or stabilization of GluA2 at the plasma membrane[54-56]. Interestingly, CFA-induced peripheral inflammation decreases NSF expression in the spinal cord[24]. Whether and how this decrease contributes to CFA-induced dorsal horn GluA2 internalization is unknown and needs additional study.

5 Changes in dorsal horn AMPAR subunit trafficking participate in central sensitization during inflammatory pain

The evidence presented so far indicates that peripheral inflammatory insults change AMPAR subunit trafficking and functional properties at synaptic and extrasynaptic

sites of dorsal horn neurons. Lastly, I will review the literature to address whether these changes are involved in the development and maintenance of inflammation-induced pain hypersensitivity. It has been reported that the induction of dorsal horn GluA1 membrane insertion by capsaicin or carrageenan correlates with the development of pain hypersensitivity[19,21]. Similarly, the GluA2 internalization and GluA1 membrane insertion that occur 1 to 3 days after peripheral CFA injection correlate with the maintenance of CFA-induced pain hypersensitivity[9,23,25]. Hence, inflammation-induced changes in dorsal horn AMPAR subunit trafficking are likely to participate in central sensitization during inflammatory pain. This conclusion is strongly supported by the following evidence. First, the activation of dorsal horn NMDA receptors and PKCα is required for inflammation-induced dorsal horn GluA2 internalization during the maintenance of inflammatory pain (Fig. 1)[4,23]; second, our recent work showed that dorsal horn PKCα knockdown not only blocks CFA-induced increases in extrasynaptic GluA1-containing and Ca^{2+}-permeable AMPARs in dorsal horn neurons, but also attenuates CFA-induced mechanical allodynia 1 day after CFA injection; third, interfering with dorsal horn GluA2 internalization by blocking the GluA2 PKCα phosphorylation site, inhibiting spinal cord PKCα, or disrupting the recruitment of PKCα to GluA2, alleviates CFA-induced inflammatory pain during the maintenance period[23,26] (Figs. 1 and 2); and fourth, peripheral CFA injection increases the number of synaptic and extrasynaptic Ca^{2+}-permeable AMPARs in the dorsal horn during the maintenance of inflammatory pain[23-25,28]. Given

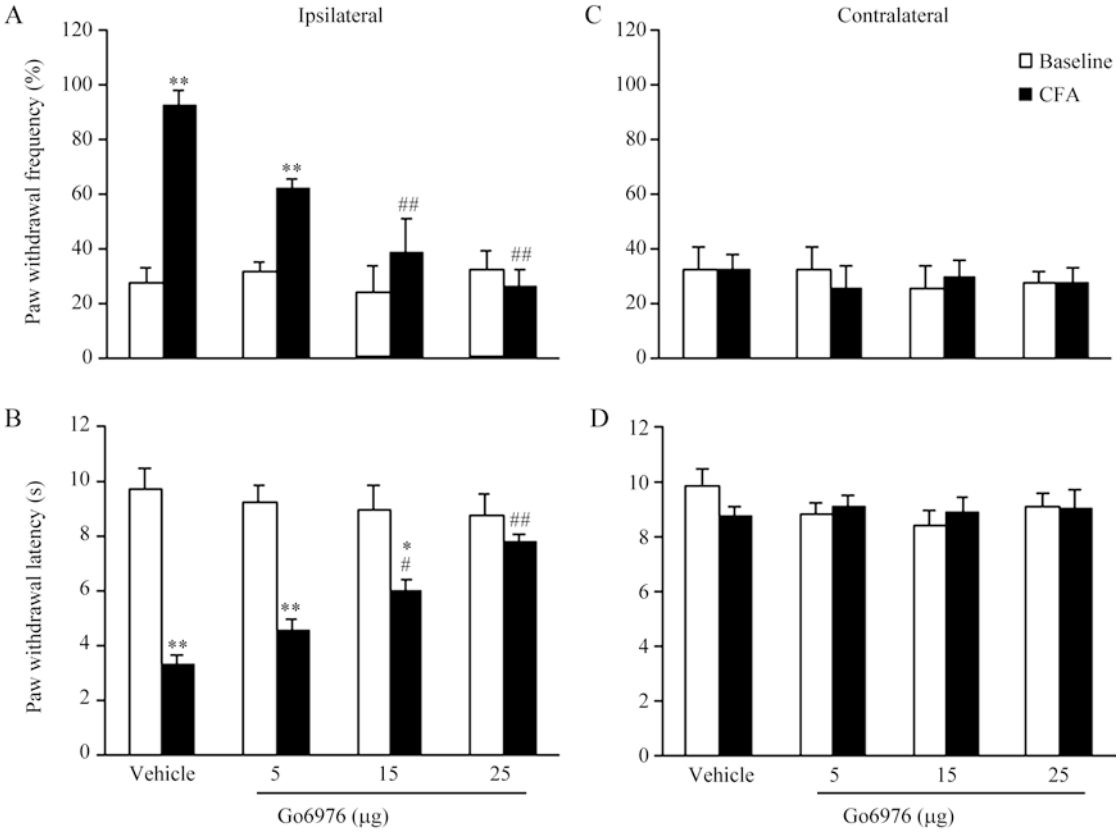

Fig. 2. Protein kinase C alpha (PKCα)-dependent mechanical and thermal hypersensitivity 1 day after complete Freund's adjuvant (CFA) injection into rat hind-paw. Two intrathecal injections of Go6976 given at a 12-h interval dose-dependently attenuated CFA-induced mechanical allodynia (A) and thermal hyperalgesia (B) on the ipsilateral side. At the doses used, Go6976 did not affect basal paw withdrawal responses to mechanical (C) or thermal (D) stimuli on the contralateral side (unpublished data). *n* = 5–6/group. $^{*}P$ <0.05, $^{**}P$ <0.01 *vs* corresponding baseline; $^{\#}P$ <0.05, $^{\#\#}P$ <0.01 *vs* vehicle group.

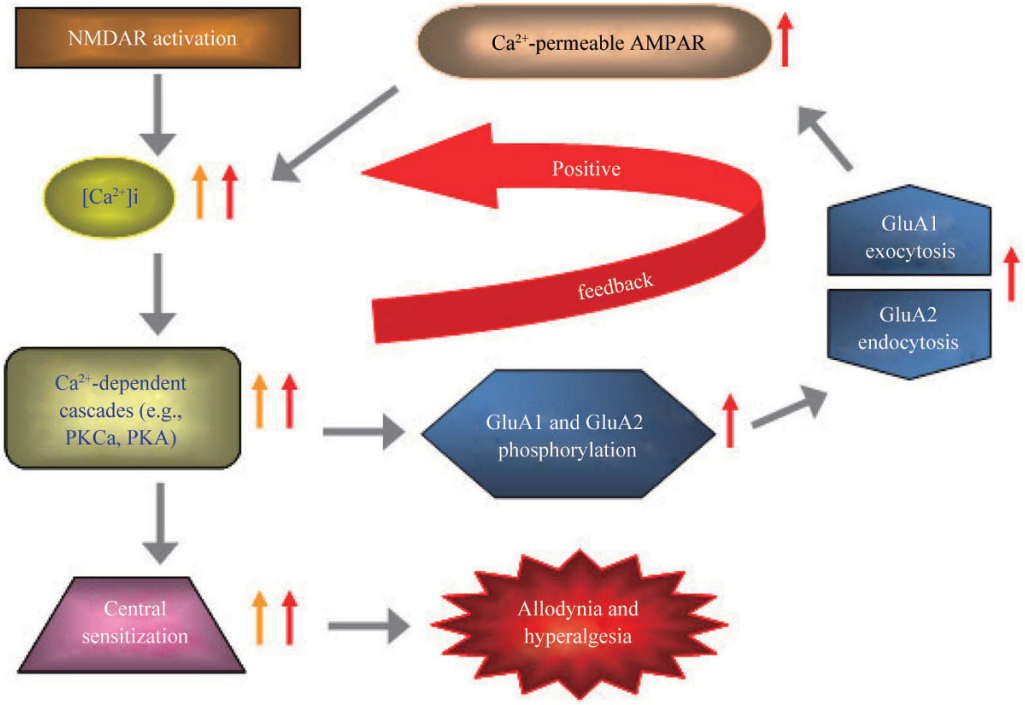

Fig. 3. A proposed model for the mechanism by which changes in the trafficking of dorsal horn α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic receptors (AMPARs) contribute to inflammation-induced central sensitization. Under inflammatory conditions, dorsal horn N-methyl-*D*-aspratic acid receptor (NMDAR) activation increases Ca^{2+} influx through NMDAR channels. The elevation of intracellular Ca^{2+} initiates or potentiates intracellular Ca^{2+}-dependent cascades, including activation of protein kinases (e.g., PKCα, PKA, or CaMKII). These cascades generate central sensitization as well as induce phosphorylation of AMPAR subunits GluA1 and GluA2 and promote GluA1 exocytosis and GluA2 endocytosis in dorsal horn neurons. The changes in AMPAR subunit composition result in an increase in AMPAR Ca^{2+} permeability in dorsal horn neurons. The increased permeability leads to more Ca^{2+} influx, which further enhances the activation of Ca^{2+}-dependent cascades. This positive feedback loop may be a key contributor to the maintenance of pain hypersensitivity under inflammatory pain conditions. PKA, protein kinase A; PKCα, protein kinase C alpha.

that the NMDA receptor, Ca^{2+}, and PKC are key players in inflammation-induced dorsal horn central sensitization[4,57,58], I propose a model in which GluA1 membrane insertion and GluA2 internalization in the dorsal horn participate in the mechanism underlying the maintenance of central sensitization in inflammatory pain (Fig. 3). In brief, after inflammation, NMDA receptor activation induces Ca^{2+} influx in dorsal horn neurons. The increase in intracellular Ca^{2+} initiates and/or potentiates various Ca^{2+}-dependent intracellular cascades (including activation of protein kinases, e.g. PKC), induces phosphorylation of both GluA1 and GluA2, and promotes GluA1 membrane insertion and GluA2 internalization. The change in synaptic and extrasynaptic AMPAR subunit composition leads to increases in AMPAR Ca^{2+} permeability. The increased permeability produces more Ca^{2+} influx, which further enhances the activation of Ca^{2+}-dependent intracellular cascades in the dorsal horn. This positive feedback loop that occurs through changes in AMPAR subunit trafficking and increases in the number of Ca^{2+}-permeable AMPARs in dorsal horn neurons may be critical for the maintenance of pain hypersensitivity in persistent inflammatory pain (Fig. 3).

6 Conclusion

Persistent (or chronic) pain is not simply the consequence of peripheral inputs or pathology but is also a reflection of changes in the plasticity of central nociceptive circuits (that is, central sensitization). These changes are sufficient to reduce the pain threshold, increase the magnitude and duration of responses to noxious input, and

permit normally innocuous inputs to induce pain sensation. Thus, central sensitization is a major contributor to many clinical pain syndromes. New research has revealed that profound changes occur in dorsal horn AMPAR subunit trafficking in persistent inflammatory pain. These trafficking changes contribute to the induction and/or maintenance of inflammation-induced central sensitization. The development of specific and selective drugs that interfere with changes in synaptic and extrasynaptic AMPAR trafficking may provide an effective novel strategy for preventing and/or treating persistent pain.

Acknowledgements: This work was supported by grants from the National Institutes of Health (NS058886 and NS072206), Rita Allen Foundation, Mr. David Koch and the Patrick C. Walsh Prostate Cancer Research Fund, and the Blaustein Pain Research Fund. The author thanks C.F. Levine, MS, ELS, for editorial assistance.

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