Targeting Trafficking of Nociceptive Receptors to Treat Chronic Pain Conditions

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Editorial

Chronic pain conditions severely deteriorate the quality of life of millions of individuals worldwide and impose a heavy financial burden on the health care system of all countries. Neuropathic pain (such as sciatica, trigeminal neuralgia, diabetic neuropathy, etc.) and inflammatory pain (such as arthritis, migraine, etc.) are common types of chronic pain conditions. It is generally accepted that the development of chronic pain states results from the peripheral and central sensitization. Peripheral sensitization refers to the hyper-excitability of nociceptive primary sensory neurons (nociceptors) while central sensitization usually refers to the hyper-excitability of nociceptive dorsal horn neurons. Peripheral sensitization is usually triggered by numerous inflammatory and pain mediators abundantly produced in inflamed tissues. Peripheral sensitization is a prerequisite for central sensitization.

It is well known that most receptors, either G-protein coupled receptors (GPCRs) or ligand gated ion channel receptors, are only functional when they reside at cell surface and are activated by extracellular ligands. Therefore, the cell surface receptors become the molecular targets of a majority of therapeutic drugs. The more abundant the receptors at cell surface, the more sensitive the receptors and the stronger the cell responses. The spatial and temporal distribution of cell surface receptor is dynamically regulated by receptor trafficking events (i.e., externalization, internalization, recycling and degradation), thus fine tuning the magnitude and time course of cellular responses to extracellular stimuli. Externalization and recycling increase the cell surface density of receptors while internalization and degradation reduce the surface receptor abundance.

Receptors are synthesized, folded and assembled in endoplasmic reticulum (ER) and then migrate from ER to the trans-Golgi network (TGN), where they attain mature status through post-translational modifications. Mature receptors then move from the TGN to their functional destination at cell surface [1]. At steady state, newly synthesized receptors are sorted into microvesicles in TGN and inserted into the cell surface through spontaneous exocytosis along the constitutive pathway. Upon stimulation, receptors undergo externalization to cell surface through regulatory pathway. Externalization increases receptor density at cell surface, thus increasing receptor sensitivity and cell response. Upon stimulation, receptors at cell surface also undergo internalization that involves phosphorylation of the receptors by G-protein receptor kinases, and subsequent binding of phosphorylated receptors to arrestins which recruit components of the transport machinery to the clathrin-coated pits and initiate the formation of the early endosome [2,3]. Internalized receptors in the early endosome are sorted to the recycling endosome for return to cell surface or to the lysosome for degradation, leading to receptor re-sensitization or desensitization [2,4].

As mentioned above, peripheral and central sensitization underlies the initiation and generation of chronic pain states. Inflammatory and pain mediators such as neuropeptides, cytokines, chemokines, neurophins, eicosanoids, etc., abundantly generated from inflamed tissues, primary sensory ganglia and spinal dorsal horn, are able to sensitize nociceptors and nociceptive dorsal horn neurons. However, the underlying mechanisms are not well understood. It is yet to be established whether modulating the trafficking of nociceptive receptors is a novel mechanism underlying pain mediators-induced peripheral and central sensitization.

Over the past decade, accumulating evidence appeared to support this theory. The long-lasting modulation of the cell surface expression of nociceptive receptor has been shown to be associated with differentially altered receptor trafficking. For example, intra-colonic injection of capsaicin induced a rapid membrane insertion of GLuR1 subunit of AMPA receptor, but not GluR2/3 in the dorsal horn neurons [5]. An inhibitor of the anterograde secretory pathway not only suppressed capsaicin-induced pain response but also prevented GluR1 membrane insertion [5], suggesting that GluR1 externalization contributes to inflammatory pain. Calcitonin gene-related peptide (CGRP) sensitized trigeminal neurons by enhancing the translocation of purinergic P2X3 receptors to the cell surface, thus increasing ATP/P2X3 mediated currents [6]. Sensitization of transient receptor potential vallinoid-1 (TRPV1) by nerve growth factor (NGF) has been shown to be mediated partly by facilitating TRPV1 membrane trafficking [7,8]. In DRG neurons, the agonist mustard oil sensitized TRPA1 channel by facilitating its trafficking to the cell surface [9]. However, other studies were focused on the internalization properties of anti-nociceptive mediators and their receptors. For example, cannabinoid-induced internalization of CB1 receptor contributes to its analgesic tolerance [10]. A different mechanism seems to account for morphine tolerance as morphine-induced μ-opioid receptor internalization and δ-opioid receptor externalization contribute to the development of its analgesic tolerance [11]. All these data indicate that modulating the trafficking of pain-related receptors is one mechanism to modify nociception, antinociception and the development of analgesic tolerance.

There are two types of evoked trafficking of nociceptive receptors exist in nociceptors or nociceptive dorsal horn neurons. The first type is the agonist induced trafficking, e.g. mustard oil induces the cell surface trafficking of TRPA1 in cultured sensory neurons and cannabinoid or morphine induces the internalization of CB1 or µ-opioid receptors. By facilitating the externalization or internalization of nociceptive receptors, the agonist either stimulates or inhibits the sensitization of nociceptors.

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nociceptive receptors TRPA1 and CB1. The second type is that pain mediators trigger the externalization of non-cognate nociceptive receptors, e.g. capsaicin induces the cell surface insertion of Glu1 receptor, NGF induces TRPV1 externalization and CGRP enhances the surface translocation of P2X3 receptors. These findings suggest that the externalization of nociceptive receptors stimulated by pain mediators through their receptor cross-talk leads to the cross-sensitization of nociceptive receptors. Like the agonist-evoked sensitization of nociceptive receptors, the cross-sensitization of nociceptive receptors mediated by other pain mediators also result in the augmentation of nociceptor sensitization and evolves into a vicious cycle via a positive feedback pathway.

To uncover the mechanisms underlying the genesis of chronic pain states, it is essential to explore the mechanisms governing pain mediators-induced trafficking events of nociceptive receptors. Therefore, blocking the externalization or promoting the internalization of nociceptive receptors in nociceptors and nociceptive dorsal horn neurons could interrupt the establishment of peripheral and central sensitizations and lead to a potential therapeutic strategy to treat chronic pain conditions. The targeting drugs could hopefully be developed into a new generation of analgesics in the future. One compound that targets pain conditions.

In summary, modulating trafficking of nociceptive receptors in nociceptors and dorsal horn nociceptive neurons induced by pain mediators is an important mechanism underlying peripheral and central sensitizations. Targeting the trafficking events of nociceptive receptors may open a novel therapeutic avenue to treat chronic pain conditions.

References