Mechanisms of Pain Sensitization and the Treatments

T. Dohi*, K. Morita, N. Morioka, M.J. Abdin, T. Kitayama, N. Motoyama, and R. Zohn

Department of Dental Pharmacology, Division of Integrated Medical Science, Hiroshima University Graduate School of Biomedical Sciences, 1-2-3 Kasumi, Minami-ku, Hiroshima 734-8553, Japan.
*corresponding author, todohi@hiroshima-u.ac.jp

ABSTRACT

Hyperalgesia and allodynia, major symptoms of neuropathic pain can results after nerve injury or chronic inflammation. Trigeminal neuropathic pain resulting from alterations in peripheral and central noxious transmission systems often produced after nerve injury by pulpectomy or tooth-extraction or from temporomandibular joint inflammation. Neuropathic also occurs in some disease state, diabetic peripheral neuropathy, post-herpetic neuropathy and trigeminal neuralgia. Allodynia is characterized by long lasting pain evoked by essentially non-painful stimuli such as just light touch and tolerance to medication with conventional analgesics.

Neuropathic pain is probably not a result of a single pathological mechanism, but the final product of an altered peripheral and central processing. Recent advances in pain research revealed that many factors derived from neurons and also non-neuronal neighboring residents participate in the initiation, development and maintenance. Among them, lipid mediators such as prostaglandins, lysophosphatidic acid and platelet-activating factor are recently found to play conspicuous roles for development of allodynia and hyperalgesia in spinal cord. Further advance by using cellular biological and molecular techniques would dig into the mechanisms underlying neuropathic pain and illustrate the new strategy and target candidate for drug development.

There are also needs for tools and methods to assess neuropathic pain, common guidelines on classification, diagnosis and management, and evidence-based approach to the treatment of neuropathic pain.

Key word: neuropathic pain, allodynia, hyperalgesia, prostaglandin, platelet-activating factor, glutamate, ATP, cyclic GMP

INTRODUCTION

Noxious stimuli to membrane of peripheral tissues produce inflammatory soup such as prostaglandins, bradykinin, histamine, serotonin, ATP, proton and NGF etc, and these mediators together activate polymodal receptors at peripheral nerve ending to evoke action potential. Primary sensory neurons mediate the transduction of the signals to central neurons, in turn, release inflammatory peptides such as substance P and CGRP from peripheral nerve ending to cause neuronal inflammation. Prostaglandins (PGs) have been recognized as the major mediators of inflammation and pain. The conversion of arachidonic acid into PGs by cyclooxgenase (COX) is the rate-limiting step. Therefore, it is believed that non-steroidal anti-inflammatory drugs (NSAIDs) produce their anti-inflammatory and analgesic effect by inhibiting COX.

Repeated noxious stimuli to peripheral tissue result in exaggerated pain sensation, hyperalgesia, one of the cardinal symptoms of persistent inflammation. This results from the increased excitability against noxious stimuli of primary afferent nociceptive nerve fibers. The different forms of sensitization can occur as the result of increased excitability of primary nociceptive afferent nerve fibers; peripheral sensitization or from alterations in the central processing of sensory stimuli, in particular, in the spinal cord dorsal horn; central sensitization.

Recent attention focusing on neuropathic pain which is often produced by peripheral nerve injury after tissue damage or surgery, injury of spinal cord, diabetic peripheral neuropathy and post-herpetic neuropathy(Fig. 1). Such patients suffer from spontaneous pain, hyperalgesia, abnormal sensation (paresthesia) and also allodynia. Allodynia, a major symptom of neuropathic pain is initiated by non-painful stimuli such as just light touch. In oral and maxillofacial region, crisis of allodynia is due to nerve injury after tooth -extraction, pulpectomy, maxillofacial surgery and temporomandibular joint inflammation. In patients of trigeminal neuralgia, it is remarkable that touch the mouth around or inside causes strong.

Neuropathic pain lasts long periods, a year or more, offers no biological advantages, impacts several millions of people around world. In addition, conventional analgesic drugs including NSAIDs and even opioids are not effective for treatment of pain, and thus the development of novel analgesics are desired.

In this content, we summarize the recent progress of two characterized pain sensitization, hyperalgesia and allodynia, from the aspect of central sensitization.

Hyperalgesia

Prostaglandins (PGs) have been recognized as the important mediators of inflammation and pain. PGE_2 plays a major role in increasing of the excitability of the peripheral ending of nociceptive nerve fibers and thereby causes primary sensitization. However, recent studies accumulate evidence which attributes to PGs a pivotal role in central pain sensitization. Peripheral inflammation leads to an increase in COX-2 expression and PGE_2 production not only in the peripheral tissue, but also in neuronal and non-neuronal cells in the spinal cord dorsal horn.

Accordingly, the analgesic action of COX inhibitors, NSAIDs which has long been thought to be primarily due to inhibition of PG synthesis in the peripheral inflamed tissue at least part of their analgesic effects arise from blockade of COX-2 in the spinal cord dorsal horn.

On the cellular and molecular mechanisms underlying PGs-mediated central pain sensitization, PGE2 via EP2 receptor stimulation facilitates the release of exitatory neurotransmitters such as glutamate or selectively activate cation channels in the superficial laminae of the spinal cord dorsal horn, the first sites of synaptic integration in the pain pathway. However, receptor subtypes, EP1, 2 or 3 in spinal cord mediated PGE2-induced hyperalgesia was dependent of dose of PGE2 or type of noxious stimuli (Ito et al., 2001). PGE2, through EP2, directly activate nonselective cation channel in deeper dorsal horn neurons, laminae III-VI, rather than those in lamina II (Baba et al., 2001). PGD2-induced hyperalgesia was blocked by NK1 but not glutamate receptor antagonists and NOS inhibitors which blocked PGE2-induced hyperalgesia.

The decrease of inhibitory neurotransmission as well as the increase of excitatory neurotransmission is important to exacerbate noxious transmission. Intrathecal injection of nociceptin, the opioid-like neuropeptide nociceptin/orphanin FQ (N/OFQ) induced hyperalgesia which was blocked by NK1 antagonist or exogenous administration of glycine, but not GABAA receptor agonist. Therefore, it is postulated that nociceptin produces disinhibition of the inhibitory glycinergic transmission in spinal cord and in turn stimulate the release of substance P or glutamate from the nerve endings of C fibers or increase in excitability of secondary sensory neurons, leading to hyperalgesia (Ito et al., 2001). Of particular interest findings, PGE2 mediates specific suppression of inhibitory glycinergic synaptic transmission onto superficial dorsal horn neurons. This inhibitory effect of PGE2 is selective onto glycinegic inhibitory neuron transmission because GABAA, AMPA and NMDA receptor-mediated transmission remained unaffected and also selective to PGE2 because PGF2α, PGD2 or PGI2 had no such effect (Ahmadi et al., 2001). Via this mechanism, PGE2 may facilitate the transmission of nociceptive input through the spinal cord dorsal horn to higher brain areas where pain becomes conscious. Inhibition of glycine receptors (GlyRs) occurred via a postsynaptic mechanism involving activation of EP2 receptors and cAMP-dependent protein kinase (PKA). Harvey et al (2004) demonstrated
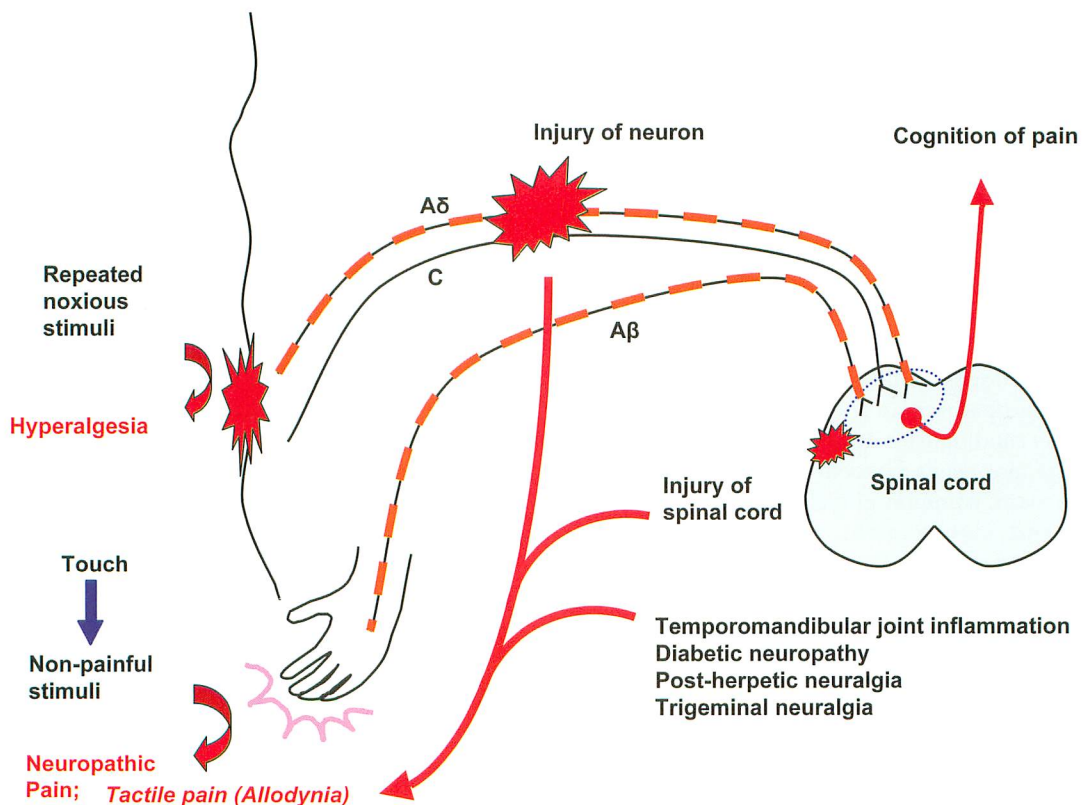

Fig. 1. Hyperalgesia and allodynia induced by nerve injury, chronic inflammation or some diseases. Repeated noxious stimuli facilitate the activation of nociceptors at the peripheral nerve endings of C or A δ sensory fibers and produce hyperalgesia through peripheral and central mechanisms. Neuropathic pain often produced by nerve injury of primary sensory neurons and spinal cord or some disease state such as temporomandibular joint inflammation, diabetes or post-herpetic infection. Allodynia is a major symptom of neuropathic pain which is evoked by essentially non-noxious stimuli such as light touch which signal is translated into spinal cord through Aβ fiber and converted into pain signals at spinal or supra spinal processing. Neuropathic pain last long periods, a year or more offers no biological advantages, impact quite lot of people around world. In addition, conventional analgesic drugs including NSAIDs are not effective for treatment of pain, and thus the development of novel analgesics is desired.

that among the GlyR subtypes, α3 subunit of GlyR could be the target molecule for PKA. GlyR α3 is distinctly expressed in the superficial laminae of the mouse dorsal horn. Mice deficient in GlyR α3 not only lack the inhibition of glycinergic transmission by PGE2 seen in wild-type mice but also show a reduction in pain sensitization induced by spinal PGE2 injection or peripheral inflammation. Therefore, the authors emphasized that GlyR α3 may provide a possible molecular target in pain therapy(Fig. 2).

Furthermore, the recent studies have revealed that spinal lipid metabolism is highly altered following persistent nociception and lipid such as lysophosphatidic acid (LPA) (Inoue et al., 2004) and platelet-activating factor (PAF) (Morita et al., 2005) are important messengers of hyperalgesia and tactile allodynia at spinal cord.

PAF is an alkyl-phospholipid, first described in stimulated basophiles, which has subsequently been found in various cells and organs including inflammation and immune related cells, vascular endothelial cells, spleen, ileum, heart, lung, kidney, cerebral cortex neurons (Ishi and Shimizu, 2000) and exocrine salivary gland (Dohi et al. 1991). PAF has been shown to be a potent lipid mediator, especially in platelet aggregation, allergy, endotoxin shock, reproduction, role in central nervous system (Ishi and Shimizu, 2000), secretory role in adrenal chromaffin cells (Morita et al., 1995) and salivary gland (Dohi et al., 1997). In particular, there is considerable evidence that PAF is an important mediator of the inflammatory response. PAF is released from a variety of inflammatory cells in response to various stimuli and the PAF receptor is constitutively expressed and regulates cellular functions in these cells. When administered intratracheally or into the pulmonary artery, PAF produces pulmonary vasoconstriction and edema (Voelkel et al., 1982; 1983), infiltration of PMNs and macrophages (Camussi et al.,
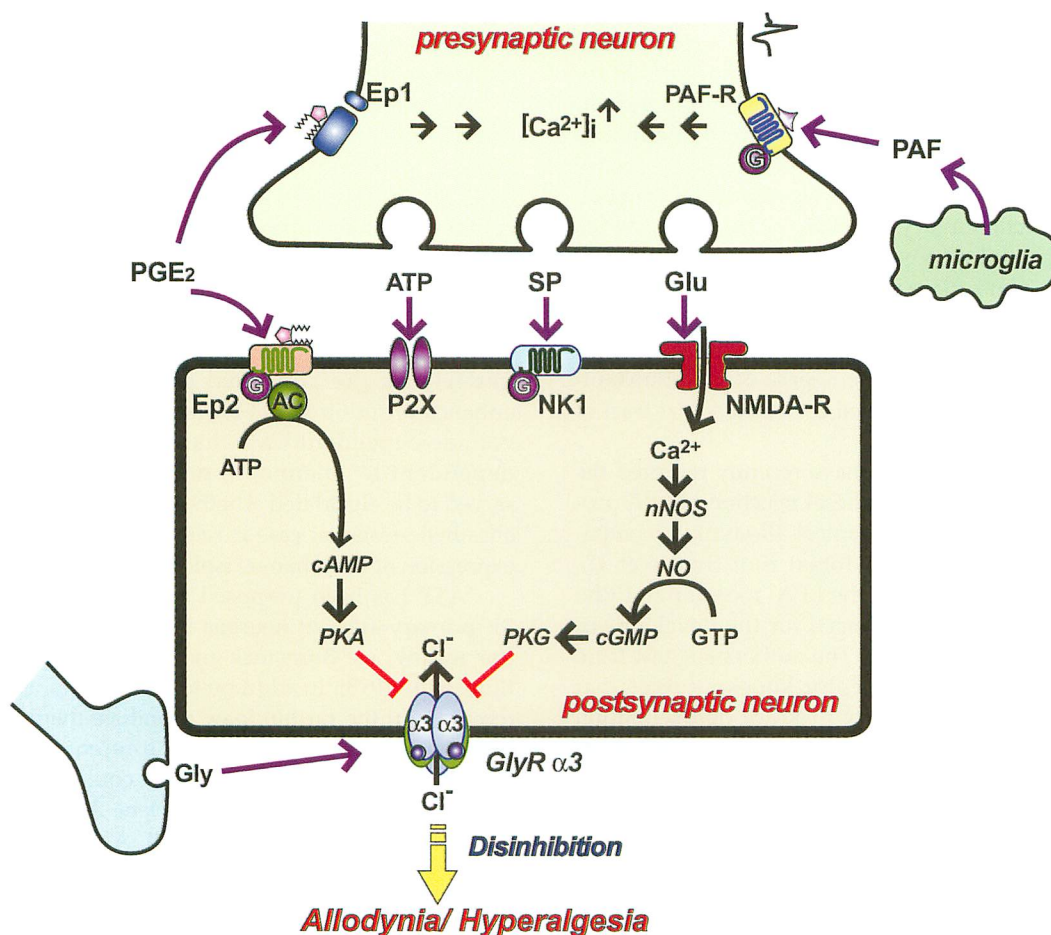

Fig. 2. Shematic model of cAMP- and cGMP-mediated regulation of nociceptive transmission at spinal cord. ATP, substance P and glutamate are the major transmitters released from primary sensory neurons at spinal cord and transduce nociceptive signals on the respective receptors at postsynaptic dorsal horn neurons. Postsynaptic PGE2/EP1 activates adenylate cyclase which stimulates the formation of cAMP from ATP. Presynaptic PAF/PAF-R stimulates the release of ATP and glutamate, resultant activation of Ca^{2+}/nNOS/NO cascade. NO activates soluble guanylate cyclase which stimulates the formation of cGMP from GTP. Glycine (Gly) is an inhibitory neurotransmitter and activates glycine receptor α3 (GlyRα3)/Cl^- channel located at superficial dorsal horn. Gly/GlyRα3 produces hyperpolarization by stimulation of extracellular Cl^- influx and inhibits excitability of dorsal horn. cAMP-dependent protein kinase (PKA) and cGMP-dependent protein kinase (PKG) phosphorylate GlyRα3 and inhibit the channel activity, resultant disinhibition leading to hyperactivity of dorsal horn, producing allodynia and hyperalgesia.

1983). Although PAF is a potent proinflammatory mediator of edema formation, PAF does not seem to be involved in pain in peripheral tissue, because PAF does not cause pain when administered peripherally. However, tactile hyperalgesia and allodynia were developed by the intrathecal administration of PAF (Morita et al., 2004). PAF content in spinal cord markedly elevated by spinal cord injury and PAF receptor antagonists blocked the expression of mRNA of ILs. These evidence suggests that PAF may be a messenger of inflammation and noxious stimuli in spinal cord.

Neuropathic pain /Allodynia

Neuropathic pain is defined as a chronic pain state that develops or persist after a primary lesion or dysfunction of the peripheral or central nervous system. In such pathological conditions when nerves are damaged through surgery, compression by bone, diabetes or infection, just touch which never produce pain in normal state, become to generate pain signals, tactile allodynia, a major symptom of neuropathic pain. Although the mechanisms for generation of allodynia are far from understanding, recent progress in our understanding of neuropathic pain come from animal models of painful peripheral nerve injury and of applying various mediators directly into spinal cord. The peripheral nerve injury models include the spinal nerve ligation (SNL) model, chronic constriction injury of sciatic nerve (CCI) model, the partial sciatic nerve ligation (PSNL) model, the spared nerve injury (SNI) model, chronic constriction of the trigeminal nerve and tibial nerve transaction (TNT) model. In these models, up- or down-regulation have been observed in diverse in the release of pain transmitters and their receptors in spinal cord and spinal tract of trigeminal nerve.

Ueda and his co-workers have recently reported the interesting evidence that intrathecal injection of LPA produced hyperalgesia and mechanical allodynia accompanied with demyelination of dorsal root (Inoue et al., 2004). LPA signaling through the LPA^1 receptor and Rho A/Rho-kinase activation is crucial for the development of allodynia and hyperalgesia. The authors suggest from current study using LPA receptor knockout mice that LPA produced by nerve injury produce demyelination and initiates neuropathic pain. This mimics demyelination following partial sciatic nerve ligation (Ueda 2005).

Although prostaglandins are key mediators of peripheral pain sensitization, recent evidence demonstrated their importance of spinal pain sensitization with different cellular mechanisms from those in periphery. Peripheral injury increased expression of COX-2 and PGE$_2$ production in spinal cord. Intrathecal injection of PGE$_2$ or PGF$_2\alpha$ into mice generate allodynia with different characteristics as described below, while PGD$_2$ is inhibitory. PGE$_2$-induced allodynia was blocked by AMPA and NMDA receptor antagonists, morphine and inhibitors of NOS and guanylate cyclase, but not by NK1 receptor antagonist (Ito et al., 2001). They suggested that PGE$_2$ stimulate EP1 receptors located on pre-synaptic to release glutamate and glutamate activates AMPA and NMDA receptors on postsynaptic neuron. PGE$_2$- and PGF$_2\alpha$-induced allodynia was disappeared in mice lacking NMDA receptors containing GluRε1$^{-/-}$ and GluRε4$^{-/-}$, respectively. Activation of NMDA receptors containing GluRε1 subunit stimulate Ca^{2+} influx following activation of PKC, Ca^{2+}/calmodulin-dependent kinase and nNOS. NO rapidly diffuse into presynaptic nerve terminals where it modulates the excitability as a retrograde messenger (O'Dell et al., 1991). It is interesting that DL-TBOA, an inhibitor of glutamate transporters, blocked the allodynia induced by PGE$_2$ or PGF$_2\alpha$ and thus glutamate transporters may play pivotal roles in the induction and maintenance of the PGE$_2$-induced allodynia (Minami et al., 2001). Capsaicin,a neurotoxin when administered neonatally, causes necrotic changes of small-sized DRG neurons, a substantial loss of C fibers in peripheral nerves, and degeneration of axonic terminals in the spinal cord substantia gelatinosa. Neonatal capsaicin treatment eliminated the PGE$_2$- but not PGF$_2\alpha$-induced allodynia (Minami et al., 1991). These results suggest that capsaicin-sensitive C fibers, usually transmit noxious stimuli may participate in PGE$_2$-induced allodynia while PGF$_2\alpha$-induced allodynia could be mediated by capsaicin-insensitive, Aβ fibers which normally transmits innocuous stimuli.

Voltage-gated sodium channels (VGSCs) play a critical role in neuronal excitability. Among subtypes of pore-forming α-subunits of VGSCs (NaV1.1-1.9), some of them (NaV1.8 and NaV1.9) are specifically localized on nociceptors. Axonal transaction triggers alterations in Na$^+$ channel expression, turning-off of previously active Na+ channel gene (NaV1.8) and turning-on of previously silent Na$^+$ channel (NaV1.3) gene. This set of molecular changes have been suggested as a key molecular event underlying the abnormal processing of pain. PGs enhance tetrodotoxin (TTX)-resistant Na$^+$ currents and voltage-dependent Ca^{2+} channel and inhibit voltage-dependent K$^+$ channel in nociceptive afferents. It is served to be elucidated whether proximate cause for local anesthetic-resistant case is relevant to such heterologous expression of Na$^+$ channel isoforms.

ATP has been proposed as a transmitter candidate for primary afferent neurons in peripheral nerve ending (for review, see Burnstock and Wood, 1996; Ralevic and Burnstock, 1998). In addition to the important role of P2X receptors in the rat hindpaw to induce thermal hyperalgesia and nociceptive behavior, a recent study demonstrated that mechanical allodynia could be induced by plantar application of α, β-methylene ATP, an agonist of P2X receptors (Tsuda et al., 2000). A number of studies support the idea that ATP may be involved in spinal nociceptive transmission via P2X receptors (Driessen et al., 1994; Li et al., 1998). We have also demonstrated that α, β-methylene ATP by intrathecal injection elicited allodynia, and PPADS, a selective antagonist for P2X receptors, blocked allodynia induced by α, β-methylene ATP, suggesting that P2X receptors in the spinal cord is involved in the development of allodynia (Fukuhara et al., 2000).

Following traumatic spinal cord injury, numerous secondary events lead to tissue degeneration extending from the initial lesion site with severe pain. PAF antagonist treatment reduces pro-inflammatory cytokine mRNA after spinal cord injury, suggesting that PAF contributes

to secondary damage after spinal cord injury (Hostettler et al. 2002). Faden and Halt (1992) administered PAF intrathecally to examine its effects in the spinal cord and found that PAF decreased blood flow in the spinal cord, motor function or survival, suggesting the role of PAF in tissue damage after spinal cord injury. Although these events establish PAF as a signaling molecule triggering the inflammatory events (Zimmerman et al., 2002), its role in the regulation of pain is not evident because PAF cause no hyperalgesia injected intradermally in healthy volunteers, although it induced potent wheal and flare responses and subsequently erythma and cellular infiltration (Sciberras et al. 1987). We have found that intrathecal injection of PAF induced tactile allodynia and hyperalgesia. Allodynia induced by PAF was blocked by PAF receptor antagonists. PAF-induced allodynia and hyperalgesia disappeared in neonatally capsaicin-treated adult mice, while allodynia but not hyperalgesia induced by intrathecally injected αβ-methylene ATP was capsaicin-insensitive. PAF-evoked allodynia is mediated by ATP and the following NMDA and NO cascade through capsaicin-sensitive fiber, different from exogenously injected αβ-methylene ATP which is insensitive to capsaicin treatment. It has been reported that ATP is co-released with other neurotransmitter such as GABA in the spinal cords (Jo and Schlichter, 1999). We have shown that PAF stimulated ATP release from cultured DRG neuron. Gu et al demonstrated that ATP stimulate release glutamate from nerve ending of DRG neurons co-cultured with dorsal horn neurons (Gu and MacDermott, 1997). Therefore, PAF stimulates the release of ATP from DRG neurons and stimulation of P2X receptors evokes glutamate release following activation of NMDA receptors and the resultant production of NO. The subsequent cascade that NO activates soluble guanylate cyclase and cyclic GMP-dependent protein kinase (PKG) play key roles for the transduction of the noxious signaling for PAF and glutamate in spinal cord. Glycine receptors are suggested as the taaget molecules for PKG to develop allodynia, because cyclic GMP-induced allodynia disappeared in GlyR α3 knock-down mice(Fig. 2). The importance of glycinergic regulation of allodynia was suggested by the observation that nicotine through α4β2 and α7nAChR system by enhancing glycinergic neuron in spinal level exert suppression on allodynia in TNT model (Dohi et al., in press).

Recent study revealed that microglia is activated and accumulated at spinal site of peripheral nerve injury and plays an important participation in pain transduction in spinal cord (Inoue et al., 2004). Tsuda et al (2003) reported that the activation of P2X4 receptors in spinal hyperactive microglia mediates tactile allodynia after nerve injury. It has been reported that PAF is released from microglia, and is also potent stimulant of microglia chemotaxis. Actually 15 minutes after the intrathecal injection of PAF, activated microglia accumulated in the superficial laminae of the mouse dorsal horn with decrement 60 min after PAF injection. PAF receptor mRNA by RT-PCR was expressed in spinal cord, DRG, cultured microglia and cultured DRG. Thus PAF may play a messenger role between microglia and neuron interaction.

Recently, it has become evident that minocyline, an antibiotics, has various biological activity, such as neuroprotective effects. Inhibitory action of minocycline on microglia activation is supposed to be one of mechanisms for neuroprotective action of minocycline. Pretreatment of minocycline did not block the initial allodynia response, however after 15 minutes facilitated the recovery from PAF-induced allodynia. Considering together with the time course of the appearance of microglia in spinal cord after injection of PAF, microglia may participate in the formation at early phase of allodynia by PAF.

Trigeminal neuropathic pain

Trigeminal neuropathic pain resulting from alterations in peripheral and central noxious transmission systems often produced after nerve injury by pulpectomy or tooth-extraction (Marbach et al., 1982; Harn and Durham, 1990; Carmichael and McGowan, 1992). If injury of branches of the trigeminal nerve occurs, sensation may be impaired, but rarely lost. Patients with such injury and pain may be more likely to report cold allodynia than patients without pain and to exhibit signs of central sensitization such as allodynia to light brushing tactile stimuli and abnormal temporal summation (Essick, 2004). It offers a most difficult challenge to therapy. In a recent development of trigeminal pain model, neuropathy is produced by loosely ligaturing the infraorbital, third branch of the trigeminal nerve of rats. Most rats of this model display signs of abnormal spontaneous pain-related behavior (Kryzhanovski et al., 1993) as well as thermal (Kryzhanovski et al., 1992; Imamura et al., 1997) and mechanical hypersensitivity (Vos et al., 1994; Benoliel at al., 2001). It has been reported in rat model with dental-injured model involving the simultaneous pulpectomy to a lower incisor and extraction of an ipsilateral upper incisor (Yonehara et al., 2002) and with loose-ligation of inferior alveolar nerves (Yonehara et al., 2003) that hypersensitivity to tactile stimulation developed on the ipsilateral side of surgery or ligation which was inhibited by MK-801 or NOS inhibitors. In such models, the number of nNOS-positive neurons increased in layers I/II of the trigeminal nucleus caudalis (SpVc) and NO production increased on the side. They suggested that NMDA receptor/NOS/NO production pathway in the SpVc may be involved in hypersensitivity to tactile stimulation developed following dental injury. Further observations that NO induced increase in excitatory amino acid (EAA) levels in the trigeminal nucleus caudalis of the rat with tactile hypersensitivity evoked by the loose-ligation of the inferior alveolar nerves suggest that NO-EAA circuit may play an important role for development and/or maintenance of neuropathic pain following dental peripheral nerve injury (Fujita et al., 2004). Phosphorylated calcium-calmodulin protein kinase IIα (pCaMKIIα) activates glutamate receptors such as AMPA receptor, and enhances its function. Ogawa et al (2005) reported that expression of pCaMKIIα increased in the trigeminal subnucleus caudalis (Vc) by inferior alveolar nerve (IAN) transaction. Intrathecal administration of KN-93, a CaMKII inhibitor, for 7 days inhibited mechano-allodynia induced by IAN, suggesting that CaMKIIα in Vc may be involved in neuropathic pain caused by IAN transaction. Increase in interleukin-6 and nerve growth factor also increased by

trigeminal nerve injury (Anderson and Rao, 2001). On the other hand, prolactin-releasing peptide (PrRP) which presents in spinal nucleus of the trigeminal nerve has potential antinociception in normal rats and antiallodynic effect in neuropathic rats (Kalliomaki et al., 2004).

Hyperalgesia and allodynia of the face often accompany migraine headache. Migraine headache is thought to result from sensitization of the spinal nuclei of the trigeminal nerve in response to sustained noxious input from distended intracranial blood vessels (Goadsby 2001).

Temporomandibular joint (TMJ) inflammation causes an increase in the excitability of the trigeminal spinal nucleus neurons. TMJ disorder patients suffer from pain against innoxious vibrotactile stimulation (Fillingim et al., 1998). This pain response occurred not only in the region of the clinical pain (face), but also on the volar forearm, where the patient reported no clinical pain. Administration of NMDA receptor antagonist, dextromethorphan attenuated the vibration-induced pain, suggesting the involvement of the NMDA receptor in this allodynia. TMJ inflammation modulates the excitability of $A\beta$-TRG neurons innervating the facial skin via paracrine mechanism due to substance P (SP) released TRG neuronal cell body. Such SP release may play an important role in determining the trigeminal inflammatory allodynia concerning the temprpmandibular disorder (Takeda et al, 2005a; 2005b).

Drugs

The management of neuropathic pain is still a major challenge to clinicians of its unresponsiveness to usual analgesics. Even the opioid drugs are considered to be less effective for neuropathic pain. Tricyclic antidepressants and anticonvulsant carbamazepine are clinically used in some case, although half of patients become refractory or intolerant to these medications (Swerdlow, 1984). The novel antiepileptic compound gabapentin was to exert some antinociceptive effect and introduced for treatment of some neuropathic pain. Gabapentin and pregabalin inhibit voltage-gated Ca^{2+} channels by binding to a high affinity binding site on $\alpha 2/\delta$ and this action is thought to be involved in their mechanisms of anti-neuropathic pain action. The antimigraine 5-HT$_{1B/1D}$ receptor agonists, sumatriptan, zolmitriptan and dihydroergotamine are suggested as analgesics to reduce certain types of trigeminal neuropathic pain in humans (Kayser et al., 2002). Recent studies suggest novel type of analgesics which activate K^+ channels and thus, indirectly prevents the activation of voltage-dependent NMDA channels. Flupirtine, muscle relaxant and neuroprotective agent and its analogue retigabine which open G-protein-activated inwardly rectifying K^+ channels and may prove to be effective for the treatment of neuropathic pain. Other Ca^{2+} channel blockers, NMDA-antagonists or GABA$_B$ agonist are under investigation for use of the medications.

CONCLUSION

Current research has shown that neuropathic pain may arise from not simple but a variety of physiological and pharmacologically distinct systems. A number of media-tors including lipid mediators released from nerve terminals or non-synaptically from neighboring glia cells, the immune system or from some others contribute to construct the pain matrix to finally build the memory of pain. Although these make difficulty for medication, the recent advances in pain research by using electrophysiological, molecular and cellular biological techniques achieve the silver lining on the mechanisms underlying initiation, development and maintenance of pain and illustrate the new strategy and target candidate for drug development.

About 20 % of diabetic patients suffer from spontaneous pain, hyperalgesia and allodynia. Most dental treatments accompany with pain and thus would make such patients more worth. However, little attention has been paid. The lack of the assessment of patients with neuropathic pain may be a cause for such careless. Several classifications are used at present as a framework for the differential diagnosis and therapy of the neuropathy. None of them covers all aspects of etiology, anatomical distribution, symptoms, and successful treatment. Diagnostic tools to more effectively select the optimal treatment for various chronic pain states are desired. Mechanism-based and symptom-oriented classification of pain is needed to create novel targets for the development of new drugs.

ACKNOWLEDGMENTS

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