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Central Sensitization and Descending Facilitation in Chronic Pain State

Emiko Senba[1], Keiichiro Okamoto[2] and Hiroki Imbe[1]
[1]Wakayama Medical University,
[2]University of Minnesota, School of Dentistry,
[1]Japan
[2]USA

1. Introduction

Physiological pain is inevitable for us to avoid harmful stimuli as one of the self-defense mechanisms. On the other hand, pathological pain, especially deep tissue pain often persists and develops into chronic pain states. Patients suffering chronic pain often complain of pain and tenderness in various parts of the body, and chronic stress often exacerbates their pain. Fibromyalgia represents the extreme end of the spectrum of chronic widespread pain syndromes. In this chapter, we address questions as follows; why deep tissue pain tends to pass into a chronic state (is deep tissue pain more unpleasant than superficial pain?), how or why the whole body aches in these patients, and how chronic stress exacerbate their pain. We speculate that persistent pain-induced brain sensitization underlies these chronic pain states. Areas involved in the emotional aspects of pain, such as the anterior cingulate cortex (ACC), insular cortex (IC), amygdala, may be sensitized. Memory of pain based on sensitization of brain areas involved in emotional response is useful for us to avoid future damage. However, in some pathological conditions, descending pain control system may switch from inhibition to facilitation, with unknown mechanism, and facilitate pain sensation and behavior. Serotonin (5-HT) may be involved in the descending facilitation in pathological pain conditions. Understanding of the etiology, pathophysiology and treatment of chronic pain states is an urgent issue from the view points of patients' quality of life and socio-economy.

2. Clinical features of chronic pain states

2.1 Clinical features of fibromyalgia syndrome

Fibromyalgia (FM) or fibromyalgia syndrome (FMS) is an intractable widespread pain disorder of unknown etiology that affects about 2-3% of population and is most frequently diagnosed in women. One unique feature of FM is its wide spread nature of pain and tenderness. Despite extensive investigations, no distinct tissue damage, structural abnormalities, or evidence for a source of chronic stimulation of pain afferents have been detected in FM patients (Meeus & Nijs, 2007). Furthermore, FM pain is diffuse and multifocal, lacks a distinct spatial localization, often waxes and wanes and is frequently migratory in nature. These features have led to the hypothesis that hyperexcitability of the

central nervous system or dysfunction of the central inhibitory system may exist in these patients. Central hyperexcitability could explain exaggerated pain and withdrawal reflex of FM patients with minimal and undetectable tissue damage, in that the nociceptive signals are amplified by the hyperexcitable neurons (Banic et al., 2004). Indeed, more numerous regions are activated in the brain of fibromyalgia patients by the same intensity of noxious heat stimuli compared to pain-free controls (Cook et al., 2004). Cognitive-behavioral therapy was shown to attenuate nociceptive flexion reflex threshold in FM patients (Ang et al., 2010). On the other hand, subtle peripheral tissue abnormalities, such as increased levels of substance P in muscle tissue, increased IL-1 levels in cutaneous tissue have also been demonstrated in FM patients (for review, see Staud & Rodriguez, 2006). Sympathetic hyperactivity, abnormal heart rate variability, has been postulated in FM patients, which may explain the multisystem features of FM and symptoms such as sleep disorders, anxiety and constant fatigue. Some people assume that FM is a generalized form of reflex sympathetic dystrophy (CRPS type I) (Martinez-Lavin, 2001, 2007). Both conditions affect mostly females and have frequent post-traumatic onset. Moreover, many features of FMS resemble those of posttraumatic stress disorder (PTSD). PTSD is highly associated with FMS in male FMS patients (Amital et al., 2006). Thus, peripheral impulse input may also play an important role in maintaining central sensitization (Staud et al, 2009). But it does not necessarily extensive, because central sensitization seems to require little sustained input for the maintenance of chronic pain state.

Several animal models for FMS or chronic widespread pain have been produced to elucidate the underlying mechanisms. Biogenic amine depletion by repeated administration of reserpine (once daily for 3 consecutive days) caused muscle and cutaneous hyperalgesia, and increased immobility time in forced swim test (Nagakura et al., 2009). Vagal dysfunction induced by subdiaphragmatic vagotomy, caused muscle and visceral, but not cutaneous, hyperalgesia (Furuta et al., 2009). Mice subjected to intermittent cold stress (4°C) exhibited prolonged bilateral allodynia (Nishiyori & Ueda, 2008).

FM is often accompanied by a variety of other symptoms (Bennett et al., 2007; Clauw, 2009; Moldofsky, 2008). Common disorders associated with fibromyalgia include chronic fatigue syndrome (21-80%), irritable bowel syndrome (32-80%), temporomandibular disorder (TMD) (75%), headache (tension/migraine) (10-80%), major depressive disorder (62%), insomnia (60-90%) and urinary disturbance (interstitial cystitis) (20-60%).

Clinical features of chronic pain states, such as FM, low back pain, TMD etc., can be summarized as follows.

1. Patients usually suffer deep tissue (musculo-skeletal) pain and tenderness.
2. Their pain and hyperalgesia is often bilateral and widespread in nature.
3. Their symptoms are aggravated by psychological/emotional stress.
4. They often accompany major depression and sleep disturbance.
5. Their symptoms are often attenuated by anti-depressant (amitriptyline) or anti-convulsant (gabapentin).

We have attempted to discuss possible mechanisms that underlie these symptoms using some animal models of chronic pain states

2.2 Why deep tissues are more frequently affected in chronic pain state?

Brain imaging studies indicate the network of somatosensory (S1, S2, IC), limbic (IC, ACC) and associative structures, such as prefrontal cortex (PFC), receiving parallel inputs from

multiple nociceptive pathways (Apkarian et al., 2005). The clinical pain processing may be different from experimental pain processing, as well as acute pain perception in normal subjects is distinct from that seen in chronic clinical pain conditions. Chronic pain engages brain regions critical for cognitive/emotional assessments (Apkarian et al., 2005; Hsieh et al., 1995). Schweinhardt et al. (2006) revealed that activation patterns of anterior insular cortex (AIC) were different in experimental and clinical pains. They divided the AIC into two parts; rostral AIC (rAIC) and caudal AIC (cAIC). Clinical pain is preferentially processed in rAIC, while experimental pain in healthy volunteers predominantly evoked cAIC. Henderson et al. (2007) compared muscular pain and cutaneous pain, by injecting 5% saline solution into muscle and subcutaneous, respectively. They found that muscular pain evoked more rostral part of the AIC than cutaneous pain did, suggesting that muscular deep pain is more uncomfortable and intractable in nature. These findings may provide us with some important cues to explain why muscular or deep tissue pain easily develops into chronic pain state.

2.3 Mirror-image pain (pain or hyperalgesia in unaffected side or area)
2.3.1 Mirror-image pain in the literature
In the literature, we can find many examples of bilateral hyperalgesia and allodynia due to unilateral neuropathy (Erichsen & Blackburn-Munro, 2002; Li et al., 2006 Yasuda et al., 2005; Yu et al., 1996;), cancer pain (Mao-Ying et al., 2006) or inflammation (Milligan et al., 2003, 2005; Shenker, 2003; Schreiber et al., 2008) in animal models and neuropathic pain (Becerra L et al., 2006; Hatashita et al., 2008; Wasner et al., 2008) , capsaicin-induced experimental pain (Shenker et al., 2008) and toothache (Khan et al., 2007) in human cases (for review see Huang and Yu, 2010). An experimental pain induced by unilateral intramuscular injection of low pH saline caused bilateral long-lasting hyperalgesia in rats (Sluka et al., 2001). They speculated that this contralateral spread of hyperalgesia was mediated by central sensitization. Milligan et al. (2003, 2005) produced sciatic inflammatory neuropathy induced by perineural injection of Zymozan to cause localized inflammation of the sciatic nerve of rats (Chacur et al., 2001). It should be noted that these animals showed unilateral (low-dose Zymozan) or bilateral mechanical allodynia (high-dose Zymozan) depending upon the intensity of the sciatic nerve inflammation induced. They also used chronic constriction injury (CCI) model, a classic partial nerve injury, to show a typical bilateral mechanical allodynia. They speculated that mirror-image pain is caused by the spreading of inflammation to the contralateral spinal cord.

2.3.2 A unilateral nerve injury-induced bilateral hyperalgesia
We reported an animal model of unilateral nerve injury-induced bilateral hyperalgesia (Yasuda et al., 2005). In the course of experiments using CCI model rats, we noticed that the nociceptive threshold to mechanical stimulation was decreased bilaterally when the unilateral sciatic nerve was accidentally tightly ligated. We also found that unilateral axotomy of the sciatic nerve exhibited bilateral hyperalgesia. Then we focused our investigation on the axotomy model. The left common sciatic nerve was exposed and tightly ligated at two locations and the sciatic nerve was cut between the ligatures (injured paw). Mechanical nociceptive thresholds were assessed by loading pressure stimulation. The lateral dorsal surface of the injured paws was hypoalgesic, while the medial dorsal paw

(innervated by intact saphenous nerve) on the injured side was hyperalgesic. Hyperalgesia in the injured paw may be mediated by intact saphenous nerve as previously described as adjacent neuropathic hyperalgesia (Markus et al., 1984). To our surprise, dorsal paws on the opposite side also showed hyperalgesia on the day of nerve injury, and these levels were maintained throughout the 14 days of experimental period (Fig. 1).
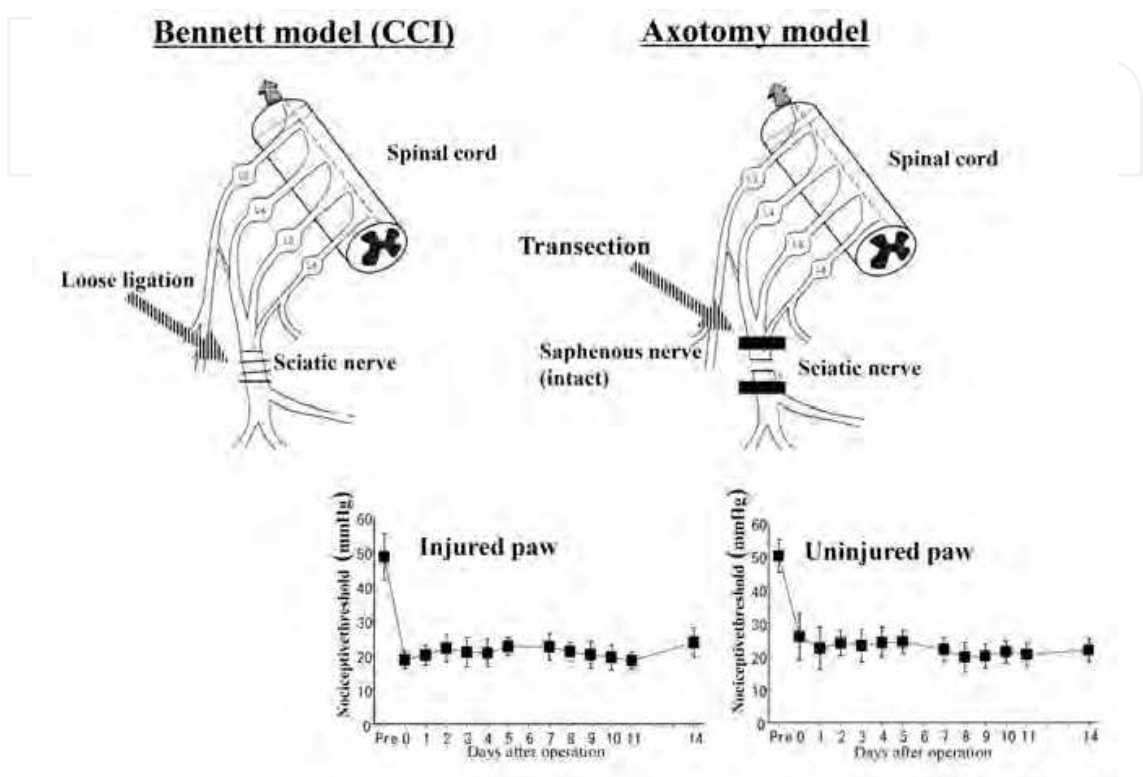

Fig. 1. Bilateral mechanical hyperalgesia observed in unilateral axotomy model rats.

Daily administration of amitriptyline resulted in significant dose-dependent normalization of the nociceptive thresholds in both paws. However, morphine was ineffective. Only the highest dose of morphine was tentatively effective (Fig. 2 A, B). Treatment with gabapentin resulted in significant dose-dependent normalization of the nociceptive thresholds in both paws, while, indomethacin, even at excessive dose was not effective at all (Fig. 2 C, D). Tail-flick latency was reduced at 4 h after axotomy, and it was maintained throughout the experiment, indicating the existence of systemic thermal hyperalgesia. We produced the same model in mice and they also showed bilateral thermal hyperalgesia.

The most prominent feature of this axotomy model is bilateral and systemic hyperalgesia in response to pressure and heat, which appeared immediately after transection of the sciatic nerve. In terms of symptoms and drug efficacy, this axotomy model resembles those seen in human patients with neuropathic pain. First, these animals exhibited mechanical and heat hyperalgesia spreading to unaffected areas, which is also observed in various chronic pain conditions in humans. Second, tricyclic amitriptyline and gabapentin, which have been accepted as first-line agents for treatment of neuropathic pain in humans, also attenuated hyperalgesia in this model. We examined the activation of microglia in the ipsi- and contralateral dorsal horn. They were activated more slowly than the appearance of the symptom and got the peak at 1 week after the transaction (Fig. 3).
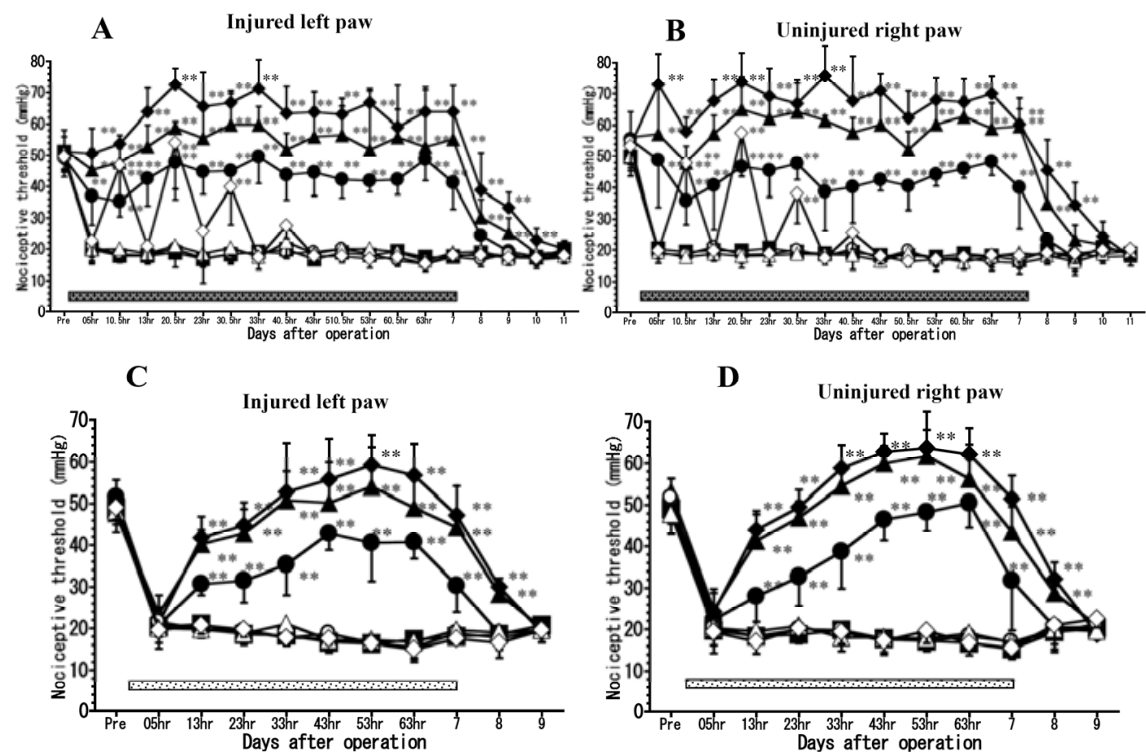
Fig. 2. Inhibitory effects of amitriptyline (A,B) and gabapentin (C,D) on axotomy-induced hyperalgesia. **P<0.01 vs. control, Dunnett's multiple comparison test.
■: control, amitriptyline ●: 25 mg/kg, p.o. ▲: 50 mg/kg, p.o. ◆: 100 mg/kg, p.o.
　　　morphine ○: 3 mg/kg, s.c. △: 10 mg/kg, s.c. ◇: 30 mg/kg, s.c. (A,B)
　　　gabapentin ●: 30 mg/kg, p.o. ▲: 100 mg/kg, p.o. ◆: 300 mg/kg, p.o.
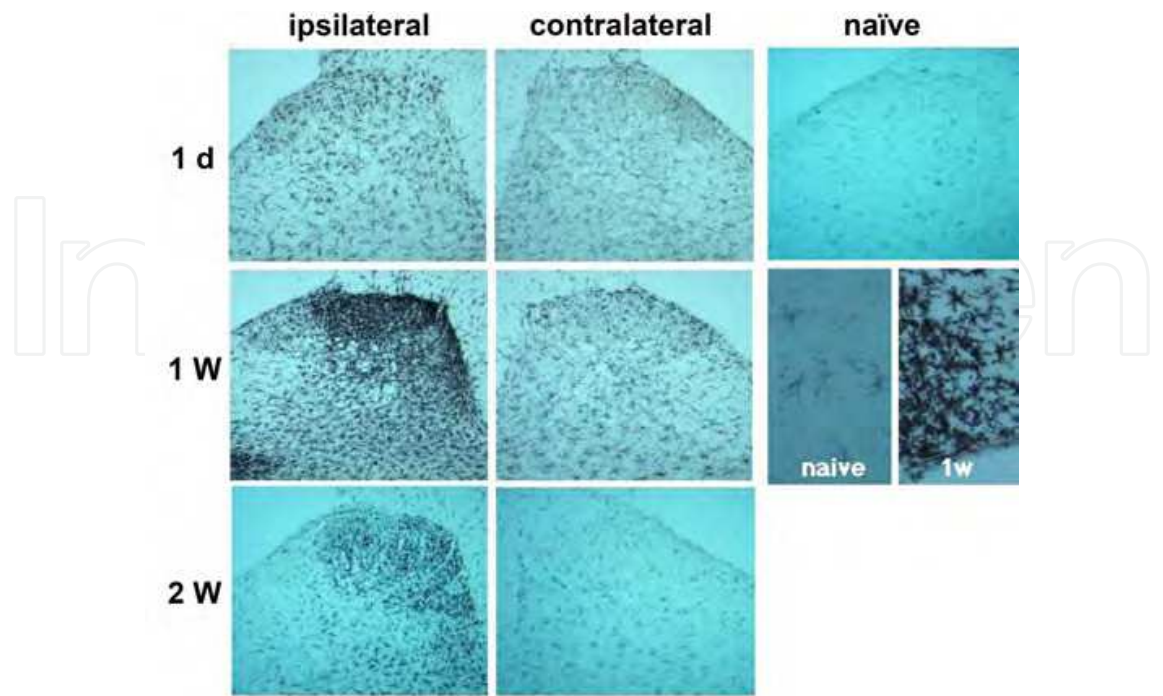　　　indomethacin ○: 1 mg/kg, p.o. △: 3 mg/kg, p.o. ◇: 10 mg/kg, p.o.(C.D)

Fig. 3. Activation of microglia (OX-42-positive) in the dorsal horn after sciatic nerve injury.

2.3.3 Possible mechanisms for Mirror-image pain

The underlying mechanisms of Mirror-image pain are still obscure, but sensitization of pain processing in the central nervous system, including the spinal cord and descending pain control system, in addition to peripheral mechanisms, have been postulated.

1. Peripheral mechanisms: Contralateral effects may be mediated by circulating factors such as cytokines, chemokines and other chemical mediators, produced in the injured tissue and/or sympatho-adrenal hormones released in response to traumatic stress.
2. Spinal mechanisms:

    #1 Neural theory: Contralateral effects may be mediated by afferent fibers projecting to the contralateral side or interposed interneurons (Koltzenburg et al., 1999). These systems may be silent in normal condition, and remodeling can be triggered by the injury.

    #2 Immune theory: Contralateral effects may be mediated by immune and glial cells, such as microglia and astrocytes, and chemical mediators derived from these cells may contribute to central sensitization through activating NMDA receptors (DeLeo et al., 2006). However, as far as our axotomy model is concerned, this theory does not seem to fully explain a prominent bilateral hyperalgesia, since only weak microglial activation was observed in the contralateral dorsal horn much later than the appearance of hyperalgesia.
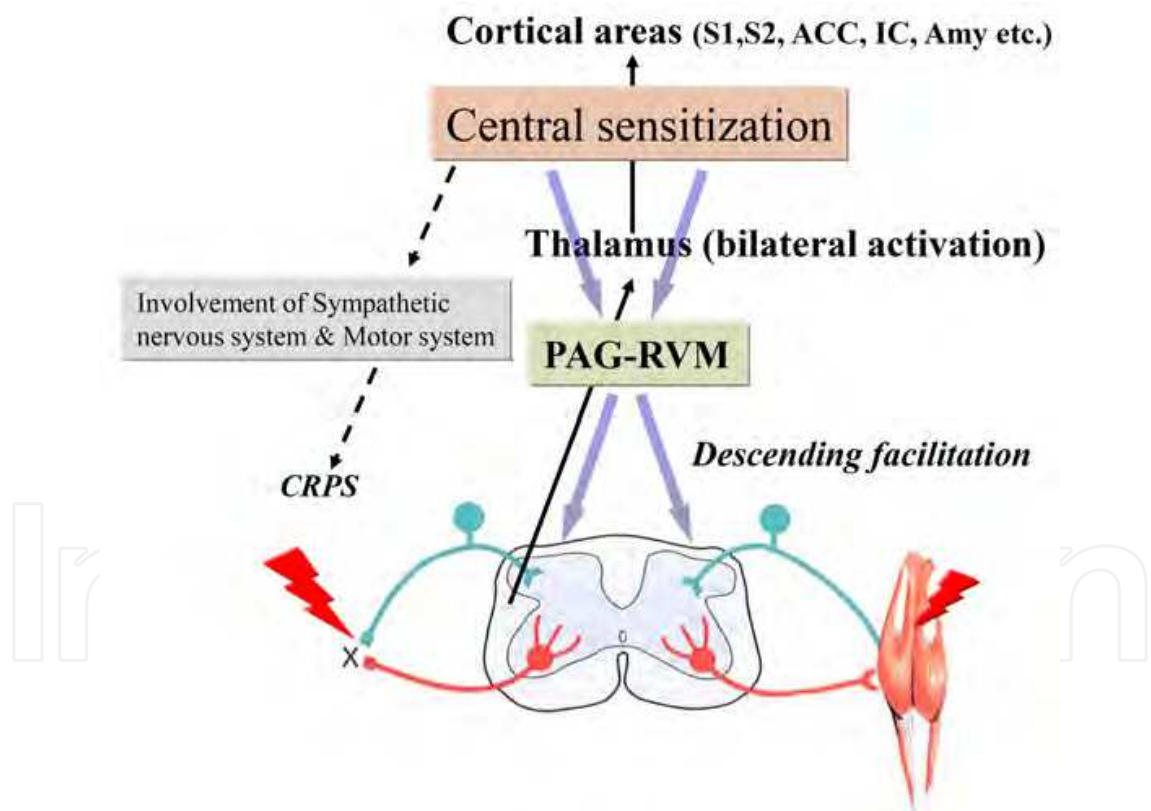

Fig. 4. Central mechanisms of Mirror-image pain.

3. Supraspinal mechanisms: Contralateral effects may be mediated by brain activation and descending facilitation in chronic pain state. Persistent noxious inputs from the periphery may sensitize certain brain areas involved in the central pain circuitry, such as ACC, IC and amygdala (Ikeda et al., 2007) (for review, see Meeus & Nijs, 2007). Activation of these areas may cause bilateral hyperalgesia via descending pain control system (Fig. 4).

Central autonomic system and motor system may also be activated and exert their influences on target tissues via visceral and somatic efferent pathways, respectively. Such pathological features may establish a syndrome called CRPS (complex regional pain syndrome) due to peripheral tissue or nerve injury.

As described above, the descending pain modulatory system may lose balance between inhibition and facilitation, turning the balance in favor of facilitation, in pathological pain conditions. There is a growing body of evidence to show that this descending facilitation plays a role in the establishment and maintenance of chronic pain state in various pathological conditions (Fig. 4).

3. How TMD patients exhibit widespread pain and hyperalgesia?

3.1 Clinical features of TMD

TMD patients, as well as those suffering FM or low back pain, often complain of persistent pain in multiple body areas (Turp et al., 1998), and evidence for generalized hyperalgesia in TMD patients has been reported (Sarlani et al., 2003). The diagnostic criteria for TMD include a pain in the TMJ and associated masticatory muscles such as masseter muscles. Several clinical studies have demonstrated decreased nociceptive threshold in remote areas in TMD patients and suggested a deficit of the endogenous pain inhibitory systems for the pathophysiology of TMD. A deficit of endogenous pain inhibitory systems including diffuse noxious inhibitory control (DNIC), has been suggested also in fibromyalgia patients (Julien et al., 2005). DNIC contributes to enhance the biologically valuable pain signals by reducing other irrelevant noise in the pain transmission system.

3.2 Hyperalgesia in remote areas in a craniofacial pain model

We developed a deep craniofacial pain model that partially mimics symptoms of TMD patients by injecting complete Freund's adjuvant (CFA) into temporomandibular joint (TMJ). Then, the influence of persistent TMJ inflammation on nociceptive responses of remote bodily areas of the rat was investigated (Okamoto et al., 2006a). Von Frey test revealed mechanical hypersensitivity in these rats at 8, 10 and 14 days after CFA injection compared to non-CFA group that had not been treated with CFA. When formalin was injected into the left hindpaw, these rats showed significantly enhanced nocifensive behavior at 10 and 14 days after CFA injection compared to non-CFA control group. The numbers of Fos-positive neurons in the ipsilateral lumbar dorsal horn were also significantly increased compared to those in non-CFA group. These findings clearly indicate that persistent TMJ inflammation may enhance nociceptive perception and nocifensive behavior in remote bodily areas.

3.3 Descending facilitation mediated by 5-HT and 5-HT3 receptors

It is well known that 5-HT plays important roles in modulating spinal nociceptive transmission. Activation of the descending serotonergic bulbospinal system modulates responses of dorsal horn neurons to noxious stimuli. Spinal cord dorsal horn as well as trigeminal subnucleus caudalis (Vc) are the major sites of 5-HT released from descending fibers from the RVM. However, controversy remains as to which types of 5-HT receptor are involved in mediating serotonergic pronociceptive or anti-nociceptive effects in this system. Nociceptive transmission in the spinal cord is modulated by the nucleus raphe magnus (NRM) and adjacent structures of the rostral ventromedial medulla (RVM). The RVM

receives projections from the periaqueductal gray matter (PAG) and sends projections to the spinal dorsal horn largely along the dorsolateral funiculus. The NRM is a major source of the descending serotonergic pathways that participate in spinal nociceptive modulation. These descending serotonergic pathways exert bi-directional control of nociception.

We further demonstrated that 5-HT3 receptors play a role in descending facilitation from the RVM to spinal dorsal horn.

In the next experiment, we injected formalin into masseter muscle in rats suffering persistent TMJ inflammation. By means of electrophysiology, we showed exaggerated responses of WDR neurons in the Vc/C2 (trigeminal subnucleus caudalis/ upper cervical spinal junction) region, and these responses were attenuated when 5-HT3 receptors were blocked (Okamoto et al., 2005b). By extracellular recordings in the Vc/C2 region, we identified two types of units; Deep-wide dynamic range (WDR) units and Skin-WDR units. Deep-WDR units have mechanoreceptive fields in the deep craniofacial tissues including masseter muscle but do not have cutaneous mechanoreceptive fields. As shown in previous studies, formalin-induced neural activities in the dorsal horn and trigeminal caudalis neurons showed a biphasic time course that is similar to that of formalin-induced behavior. Deep-WDR unit discharges evoked by the formalin injection into masseter muscle were significantly enhanced in the late phase in CFA-injected day 7 group. Discharges of Skin-WDR units evoked by the noxious pinch stimulation to facial skin in CFA-injected day 7 group were also significantly enhanced compared with those in non-CFA-injected group. Topical administration of central 5-HT3 receptor antagonist, tropisetron, onto trigeminal Vc/C2 region significantly reduced both formalin-evoked Deep-WDR unit and pinch-evoked Skin-WDR unit discharges in non-CFA and CFA day 7 groups (Fig. 5).
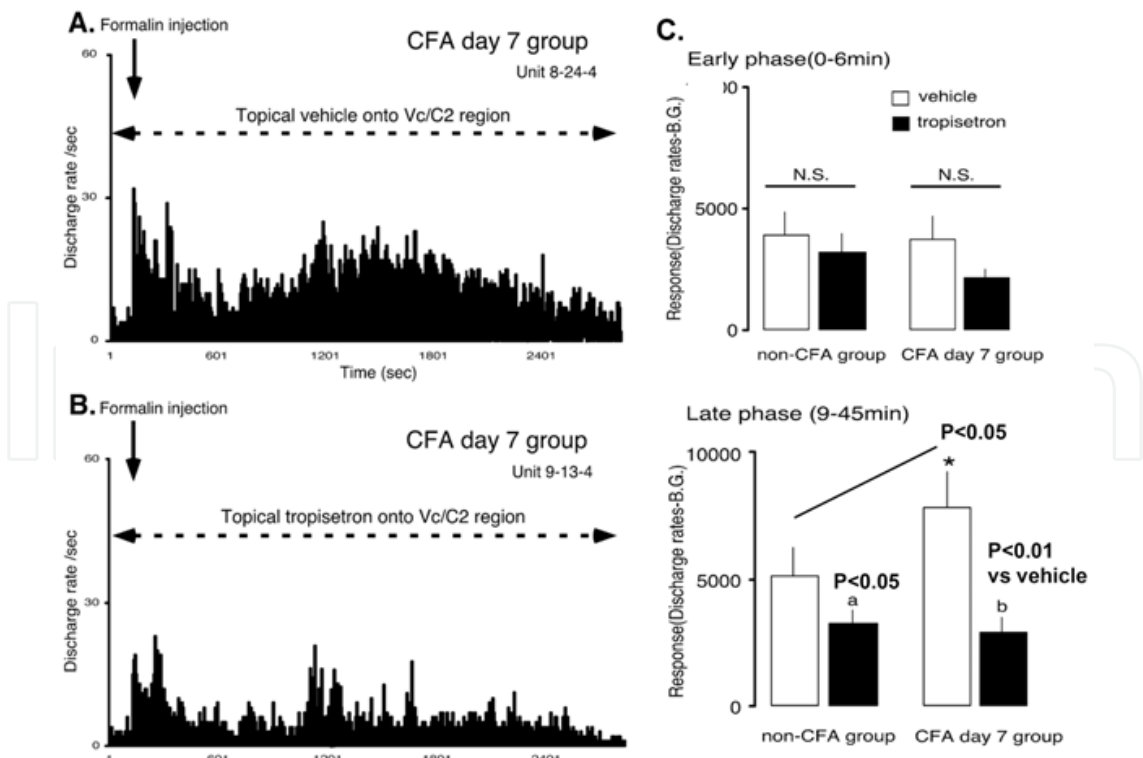

Fig. 5. The effects of topical application of tropisetron onto the Vc/C2 region on the early and late phases of Deep-WDR unit responses evoked by formalin injection.

Therefore, it is concluded that 5-HT derived from descending fibers from the RVM activated spinal/trigeminal dorsal horn neurons via 5-HT3 receptors and facilitated pain behavior (Okamoto et al., 2005b). Recently, Wei et al. (2010) showed the essential role of 5-HT in this system in pathological pain conditions by selectively blocking 5-HT production in the RVM. As for 5-HT2A receptors, we demonstrated that this receptor subtype is involved in the suppression of nociceptive processing and behavior using the deep craniofacial pain model (Okamoto et al., 2007). Most of 5-HT2A receptor-immunoreactive neurons in the superficial Vc/C2 region were glutamic acid decarboxylase (GAD)-positive, i.e. inhibitory interneurons (unpublished observation of K.O.). On the other hand, the majority (about 87%) of 5-HT3 receptor-immunoreactive dorsal horn axons seem to be derived from GAD-negative, presumably excitatory interneurons (Maxwell et al., 2003). Therefore, 5-HT2A and 5-HT3 receptor subtypes may exert opposite influences on pain transmission in the dorsal horn (Fig. 6), while we have shown, in the periphery at the level of sensory nerve terminals, these two receptors potentiate hyperalgesia in pathological conditions (Okamoto et al., 2004, 2005a, 2006b). 5-HT2A receptors are exclusively involved in the potentiation of inflammatory pain (Okamoto et al., 2002).
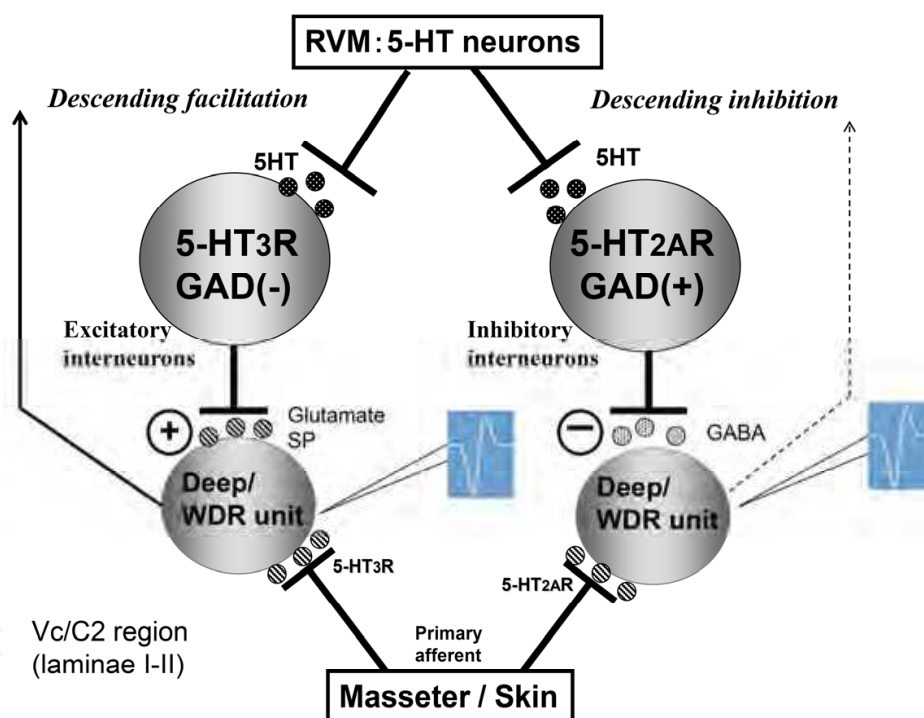

Fig. 6. Descending facilitation and inhibition differentially mediated via 5-HT3 receptor and 5-HT2A receptor expressing interneurons in the dorsal horn.

4. How is chronic pain state aggravated by stress?

4.1 Stress-induced analgesia and hyperalgesia

Acute stress is generally considered to suppress pain, which is called stress-induced analgesia (SIA). We usually feel less pain when we are injured in a battle or in a sport game. On the other hand, repeated exposure to non-noxious situation, such as chronic restraint stress, forced swim stress, cold environment or social defeat, can elicit hyperalgesia and allodynia in experimental animals (for review, see Imbe et al., 2006). It is well known that

chronic psychoemotional stress and anxiety enhance pain sensitivity in human (Ashkinazi & Vershinina, 1999; Rhudy & Meagher, 2000). Stress has also been found to exacerbate and could contribute to the etiology of chronic painful disorders, such as, fibromyalgia (Clauw, 2009; Wood, 2004), low back pain (Pincus et al., 2002), irritable bowel syndrome (Delvaux, 1999), rheumatoid arthritis (Herrmann et al., 2000) and headache (Nash & Thebarge, 2006).

A variety of environmental and/or psychological stressful stimuli have been shown to affect pain sensitivity. Some kinds of acute stress and most of chronic stress increase pain sensitivity. These phenomena are termed stress-induced hyperalgesia (SIH) (Imbe et al., 2006). Acute exposure to emotionally arousing non-noxious stress, such as inescapable holding, novel environments or vibration, produces an immediate and transient hyperalgesia (Jorum, 1988; Vidal & Jacob, 1982).

A line of evidence suggests that chronic stress induced by repeated exposure to cold environment (Satoh et al., 1992), restraint (Gameiro et al., 2005, 2006; Imbe et al., 2004) and forced swim (Quintero et al., 2000, 2003; Suarez-Roca et al., 2008) also produces relatively persistent hyperalgesia, which seems to mimic the human chronic pain condition. For example, chronic restraint stress (1h daily for 4 days) produced mechanical allodynia and hyperalgesia in formalin test in rats (Bardin et al., 2009). Repeated swim stress (10-20 min daily for 3 consecutive days) induced hyperalgesic responses to formalin injection into hindpaw and increased c-Fos expression in the spinal dorsal horn compared to those observed in naïve rats or rats subjected to sham stress (Quintero et al., 2003). Repeated cold stress (4^0C or -3^0C for 5 days) induced bilateral deep mechanical hyperalgesia in rats (Nasu et al., 2010). Although in these animal models dysfunctions of several neurotransmitter systems have been shown pharmacologically to be involved in SIH, the responsible neural circuits remain elusive.

4.2 Proposed mechanisms for stress-induced hyperalgesia

There may be two hypotheses to explain the mechanisms of stress-induced hyperalgesia; one is peripheral theory and the other is central theory. Water avoidance stress model, a psychological stress, induced muscle hyperalgesia and increased muscle nociceptor activity, including increased action potentials and conduction velocity (Chen et al., 2011). These authors speculated that these peripheral mechanisms may contribute to the stress-induced chronic widespread pain, like fibromyalgia, and supported peripheral theory. Repeated sound stress also activates hypothalamo-pituitary-adrenal and sympathoadrenal axes, and enhances mechanical hyperalgesia induced by inflammatory mediators. The released glucocorticoids and catecholamines cause long lasting alterations in intracellular signal pathways in primary afferent nociceptor (Khasar et al., 2005, 2008, 2009). Spinal mechanism, i.e. reduced γ-aminobutyric acid (GABA) release in the dorsal horn of rats subjected to repeated forced swim stress is also implicated in the SIH (Suarez-Rosa et al., 2008). As central mechanisms of SIH, descending pain modulatory system from the RVM to the spinal dorsal horn may play a key role. Initially this system was considered to be solely inhibitory (Basbaum & Fields, 1984). However, it gradually became evident that this descending system from the RVM exerts bidirectional (facilitatory and inhibitory) control of nociception (Porreca et al., 2002; Ren & Dubner, 2002). Many studies have reported the participation of descending facilitatory input from the RVM in inflammatory and neuropathic pain conditions. Recent studies have demonstrated that inflammatory (Sugiyo et al., 2005), neuropathic (Burgess et al., 2002), cancer (Donovan-Rodriguez et al., 2006) and visceral pains (Vera-Portocarrero et al., 2006) are linked to the activation of descending facilitatory pathway from the RVM. Burgess et al. (2002) showed that this system maintains, but does not

initiate, neuropathic pain. At the cellular level, both on- and off-cells, but not neutral cells, in the RVM are sensitized to mechanical stimuli after nerve injury (Carlson et al., 2007). As to the contribution of the RVM to stress-induced pain modulation, previous studies have shown that the RVM is involved in SIA (Foo & Helmstetter, 2000; Mitchell et al., 1998). Balance between inhibition and facilitation may determine the outcome effects of stress on pain behaviors.

4.3 Descending facilitation in chronic stress and chronic pain state

We have examined possible involvement of descending facilitation in chronic stress-induced hyperalgesia. Briefly, rats were stressed by restraint daily for 6 h. In the acute stress model, they were exposed to a single restraint. In the chronic stress model, they were repeatedly exposed to daily restraint for 1, 2 or 3 weeks. The control group was not subjected to restraint. Tail-flick latency (TFL) and activation of extracellular signal-regulated kinases (ERK) in the RVM were assessed. Acute restraint stress (6 h, 1 day) obviously increased TFLs. Conversely, chronic restraint stress (6 h/day, 2- or 3-week) caused a reduction in TFLs (Fig. 7). Only a few phosphorylated-ERK (p-ERK)-immunoreactive (IR) neurons were observed in the RVM of the control and acutely restraint rats, but 3-week restraint stress produced robust increase in p-ERK-IR in the RVM (Fig. 8). On the other hand, c-Fos expression was increased only in the brain of acutely stressed animals. C-Fos response was dramatically decreased when stressful stimuli were repeated as we have shown previously (Senba & Ueyama, 1997; Umemoto et al., 1996).

Especially 3-week restraint stress induced about 60% increase in the number of p-ERK-IR neurons in the RVM, compared to the control rats. Since about 20% of the total RVM neurons are serotonergic, we examined immunohistochemical colocalization of p-ERK and 5HT. The majority of p-ERK-IR neurons also expressed 5HT-IR. The incidence of p-ERK-IR in RVM 5-HT neurons was doubled after 3-weeks of restraint (30.2%) compared to control rats (14.2%). Western blot analysis showed that the level of TPH in the 3-week restraint rats was significantly increased (130%, n=4) compared to that in the control rats (100%, n=4, P<0.05) (Fig. 9) (Imbe et al., 2004).
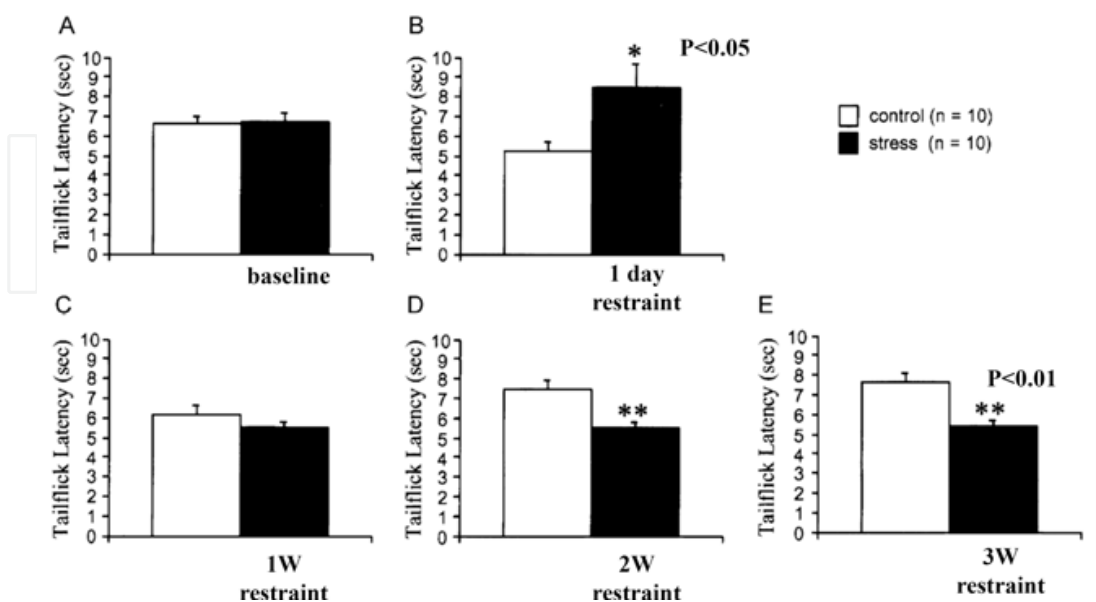

Fig. 7. Effects of acute and chronic restraint stress on tailflick latencies, showing stress-induced analgesia (acute) and stress-induced hyperalgesia (chronic).
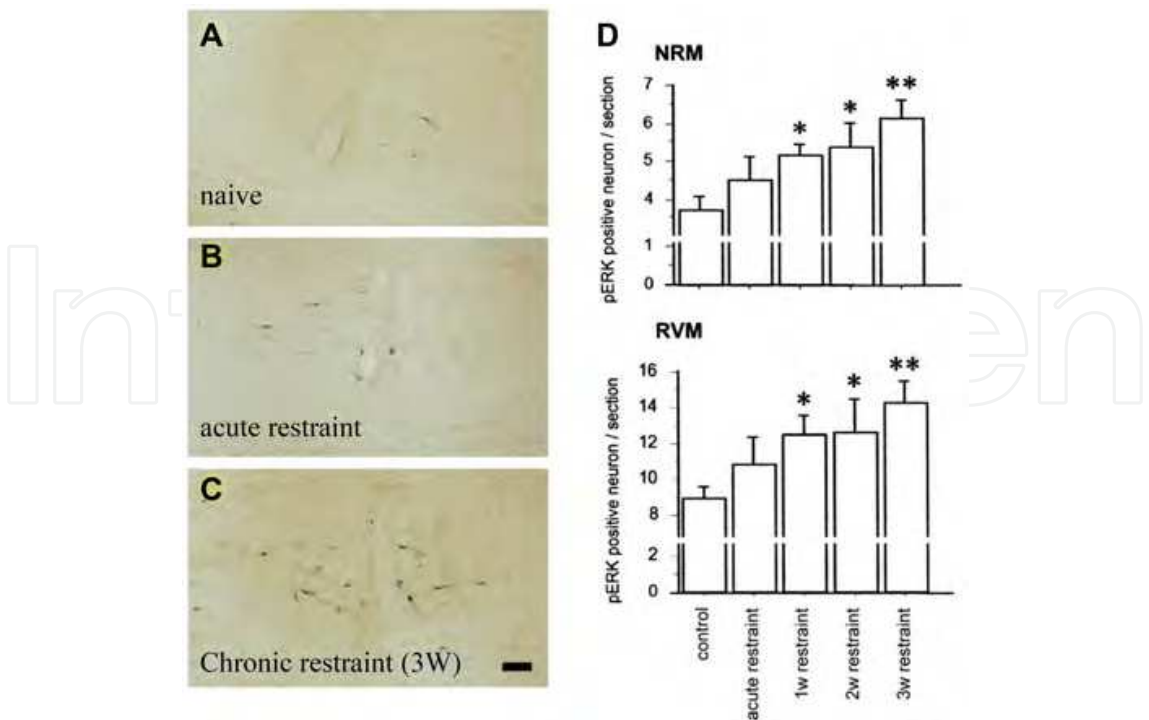
Fig. 8. Numbers of p-ERK-positive neurons in the RVM in control and stressed rats.
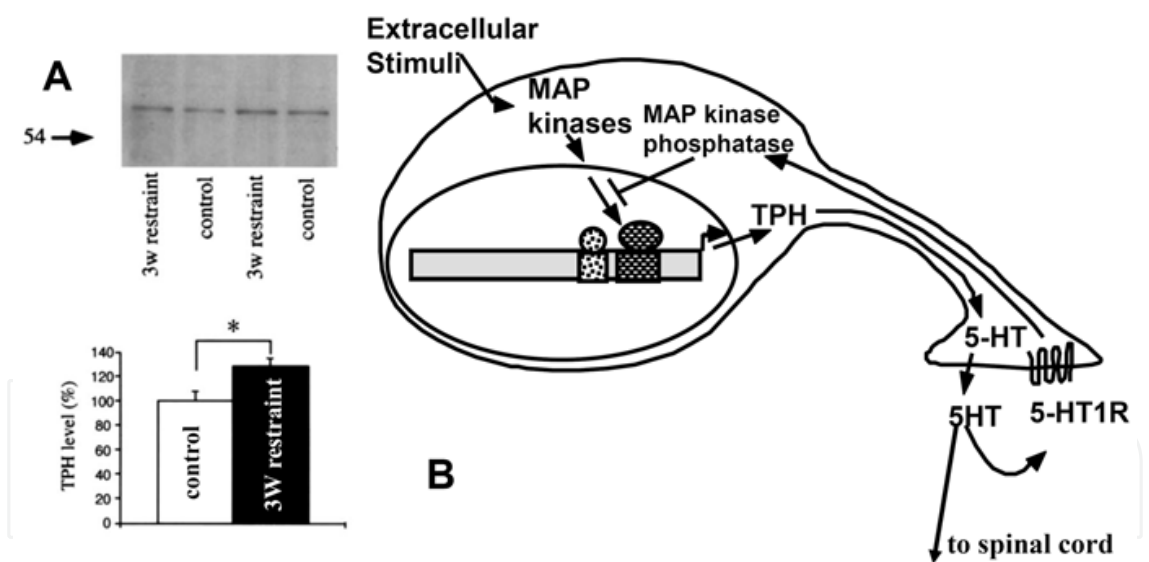

Fig. 9. Effects of 3-week restraint stress on the level of TPH (A). Activation of ERK may increase the transcription of TPH in 5-HT producing RVM neurons (B).

We have previously showed that activation of ERK in the RVM is involved in thermal hyperalgesia during peripheral inflammation (Imbe et al., 2005, 2008, 2011). We also showed that microinjection of MEK inhibitor, U0126, into the RVM attenuated the hyperalgesia due to CFA-induced peripheral inflammation. Recently it has been demonstrated that activation of ERK in the RVM also contributes to persistent neuropathic pain (Geranton et al., 2010). Under the special condition of chronic restraint stress, persistent ERK activation induced by chronic stress may increase the transcription of tryptophan hydroxylase (TPH), a rate-

limiting enzyme in serotonin biosynthesis (Wood & Russo, 2001), leading to central sensitization of dorsal horn neurons via descending serotonergic facilitatory projection (Fig. 9). Moreover, in the same study we observed p-ERK-immunoreactivity was dramatically decreased in the locus coeruleus (LC) of chronically stressed animals (Imbe et al., 2004), suggesting that descending noradrenergic inhibition to the spinal dorsal horn is decreased. This may also contribute to the chronic stress-induced hyperalgesia.

We showed another example of stress-induced hyperalgesia and enhancement of pain behavior, in which rats were subjected to forced swim stress for 3 days (Imbe et al., 2010). These animals showed prolonged nocifensive behavior in Formalin test. The destruction of the RVM with ibotenic acid almost completely prevented the enhancement of formalin-evoked nocifensive behavior following the forced swim stress (Fig. 10).

As a summary, chronic restraint stress induced thermal hyperalgesia in rats (Imbe et al., 2004), in which p-ERK and levels of TPH were increased in the RVM. 5HT released from the bulbospinal neurons may exert facilitatory effects on spinal nociceptive processing probably through 5HT3 receptors (Okamoto et al., 2005b; Suzuki et al., 2002, 2004). We also demonstrated that descending facilitation from the RVM is required for the enhancement of formalin-evoked nocifensive behavior following repeated forced swim stress (Imbe et al., 2010). These findings clearly indicate that stress-induced brain sensitization may aggravate pain and hyperalgesia, through PAG-RVM pathway. Molecular and cellular mechanisms of stress-induced central sensitization are still obscure, but it has been demonstrated that chronic stress induces dendritic remodeling of cortical (Radley et al., 2004), hippocampal and amygdaloid neurons (Vyas et al., 2002).
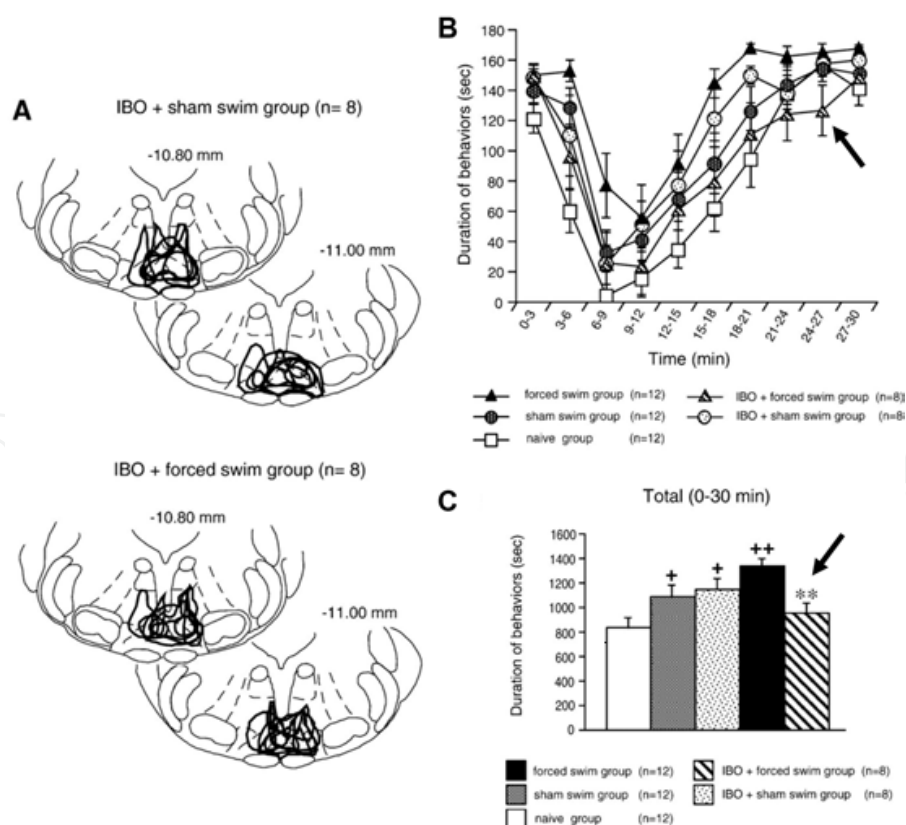

Fig. 10. Destruction of the RVM with ibotenic acid (IBO) (A) blocks the enhancement of formalin-evoked nocifensive behavior in rats subjected to forced swim stress (arrows in B, C).

Now it is obvious that PAG-RVM-spinal (or trigeminal) dorsal horn system is a final common pathway for descending pain modulatory system. A line of experimental evidence suggests that the RVM is a target of descending fibers from upper brain regions to induce SIH. The dorsomedial nucleus of the hypothalamus (DMH) plays important roles in mediating neuroendocrine, cardiovascular and thermogenic responses to emotional stressor. Activation (disinhibition) of the DMH induced a robust activation of ON-cells, suppression of OFF-cells in the RVM and behavioral hyperalgesia in rats (Martenson et al., 2009). Other brain regions that are critical to emotional processes, such as amygdala, lateral hypothalamus, ACC and PFC, also modulate nociceptive behavior by affecting the activity of RVM (Calejesan et al., 2000; Holden and Pizzi, 2008; Hutchison et al., 1996; McGaraughty & Heinricher, 2002, McGaraughty et al., 2004).

Thus, brain activation due to chronic emotional stress in addition to persistent pain in the peripheral tissue may add widespread nature to the chronic pain state. In the situations where threats are repeated, a shift towards descending facilitation of pain may be required to enhance vigilance in order to ensure survival.

5. Plastic changes in the ACC and chronic persistent pain

5.1 Mechanisms of central sensitization

Central sensitization has been defined as "an enhanced responsiveness of nociceptive neurons in the CNS to their normal afferent input" by the International Association for the Study of Pain (IASP). Synaptic plasticity in the cortex as well as in the spinal dorsal horn is believed to be important for the amplification of painful information in chronic pain conditions. The ACC is found to be a key area that links various noxious and painful stimuli to emotional responses. Central sensitization of this area may lead to chronic pain, as well as pain-related cognitive emotional disorders.

There are two major mechanisms that contribute to central plasticity: first, it is well known that LTP, which includes postsynaptic glutamate receptors, such as NMDA and AMPA receptors, and downstream signaling molecules, various kinds of kinases, increased presynaptic glutamate release, provides basic neural mechanism for learning, memory, and chronic pain (Sandkuhler, 2007). The mechanisms of LTP in the ACC have been extensively studied (Kim et al., 2010; Zhuo, 2007, 2008). Second, decreased inhibitory mechanisms by GABA may also contribute to the central sensitization. Recently it has been clearly demonstrated that under neuropathic pain conditions, membrane-bound GABA transporter-3 (GAT-3) on activated astrocytes were significantly increased in the ACC, leading to a decrease in extracellular GABA levels and an increase in neuronal activation in this area (Narita et al., 2011). These long-term synaptic changes help the brain to recognize the changing environment, to gain the ability to respond properly to it and avoid danger in the future. However, in the case of permanent injury, brain fails to distinguish acute physiological pain and chronic pathological pain, and respond similarly, subjecting us to useless, only harmful exaggerated pain state.

5.2 Mechanisms of insomnia in chronic pain patients

One of the common complaints and sufferings of people with chronic pain, including FM, is insomnia (Moldofsky, 2008; O'Brien et al., 2010). Cortical GABAergic neurons play important roles in sleep/wake regulation (Gottesmann, 2004; Kilduff et al., 2011), and

disturbance of this system may lead to the pathogenesis of insomnia in these patients. In the experimental model mice for neuropathic pain, an increase in wakefulness and a decrease in non-rapid eye movement sleep during day time, in which mice are supposed to be drowsy or sleeping, have been demonstrated by means of EEG analysis (Takemura et al., 2011). Under these conditions, as mentioned above, GAT-3 on activated astrocytes were increased in the ACC, and extracellular GABA levels in this area after depolarization were rapidly decreased (Narita et al., 2011). Furthermore, sleep disturbance induced by sciatic nerve ligation was improved by the intra-cingulate cortex injection of a GAT-3 inhibitor. These findings provide novel evidence that sciatic nerve ligation decreases extracellular-released GABA in the ACC of mice, which may, at least in part, explain the insomnia in patients with neuropathic pain. On the other hand, it should be noted that sleep disturbance, i.e. REM deprivation, itself may reduce pain threshold (Hakki Onen, 2001).

5.3 Treatment of chronic pain with gabapentin

Recently brain hyperactivity in neuropathic pain model mice in response to painful thermal stimulation has been examined using functional MRI (fMRI) (Takemura et al., 2011). Compared to sham-operated animals, exaggerated BOLD signals in the brain regions, such as the S1, ACC and medial/lateral thalamus, of animals subjected to nerve ligation were observed. Injection of gabapentin (GBP) (60 mg/kg, i.p.) dramatically reduced the nerve injury-induced brain hyperactivity. At the same time, thermal hyperalgesia these animals showed was also normalized by GBP. Changes in EEG patterns identified in these mice during light phase were also attenuated by GBP treatment (Takemura et al., 2011).

The site of action of GBP is still obscure, although GBP was shown to block the function of voltage-gated calcium channels (VGCCs), by binding to the α2δ-1 subunits. VGCCs play an essential role in controlling neurotransmitter release, neuronal excitability, and gene expression in the nervous system. In VGCCs, α1 subunit harbors the channel pore and gating machinery, while accessory subunits, α2δ-1, affect channel kinetics, contributing to the trafficking and insertion of main α1 subunit into the membrane.

One of the possible sites of action of GBP is spinal dorsal horn, in which α2δ-1 subunits are expressed on the primary afferent terminals (Li C-Y et al., 2004). Supraspinal hypothesis has also been postulated. GBP may inhibit the release of GABA, and disinhibition of LC neurons may potentiate descending inhibition (Tanabe et al., 2008). There may be numerous candidates for possible sites of action of GBP, since α2δ-1 subunit mRNAs are widely distributed in supraspinal pain-related areas, in addition to DRG and spinal dorsal horn (Cole et al., 2005). Indeed, GBP has marked positive and negative effects on BOLD signal intensity in a number of pain-related supraspinal areas (Governo et al., 2008), supporting its well-described analgesic effects both in animal models and patients of chronic pain states.

6. Conclusion

1. Mirror-image pain and stress-induced hyperalgesia may be induced by central sensitization and subsequent descending facilitation.
2. Brain hyperactivation, systemic pain and sleep disturbance were attenuated by gabapentin. Central sensitization could be a treatment target in patients suffering chronic widespread pain, such as fibromyalgia.

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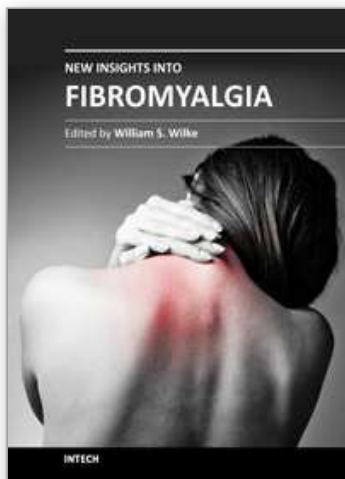
New Insights into Fibromyalgia

Edited by Dr. William S. Wilke

Given the potential problems that can obscure any scientific enterprise, inconsistent results across studies are bound to occur. How are we to decide what is true? Let's turn to philosophy for a reasonable answer. The mathematician-philosopher Bertrand Russell approached a similar problem in his monograph The Problems of Philosophy (Russell B, 1912). He addressed the following question: How do we know that anything is "real"? Is the only reality subjective and simply in our minds, as Bishop Berkley challenged, or can we mostly believe the objective reality? His pragmatic answer: All possibilities may be true, but when the preponderance of evidence indicates that objective reality and knowledge are the most probable case, go with it. If the preponderance of all evidence about the clinical description of fibromyalgia and it's pathogenic mechanisms and treatment strategies indicate a highly probable interrelated hypothesis, go with it. The direction of the literature on the whole trumps the less likely tangents. At the same time, remember Bertrand Russell and his pragmatic answer, and keep an open mind.

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