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Chronic pain syndrome (CPS) and its interventions

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PAIN MODULATORY MECHANISMS

Chronic pain are estimated to affect up to 40% of the adult population[1]. Chronic pain state or chronic pain syndrome (CPS) can have a harmful effect on people's lives, depressing their ability to work and carry out everyday activities, and disturbing their relationships with family, friends, and employers[2]. The CPS also imposes large economic burdens on society[3,4].

Our understanding with regard to CPS has increased substantially in recent years[5,6]. Much of its pathophysiology, however, is still elusive, which may lead to unsatisfied treatments for patients. Many studies indicate that the most part of prominent symptom complex of CPS is neurogenic even in the peripheral origin. The pain seems to result from neurochemical imbalances not only in peripheral nervous system (PNS) but also in the central nervous system (CNS) that lead to a central facilitation of pain perception characterized by allodynia and/or hyperalgesia.

Human neuroimage studies support these findings, showing that the CPS is associated with abnormal processing of painful stimuli in the CNS. Functional magnetic resonance image (fMRI) studies of the brain demonstrate that a pain response can be elicited in patients with chronic pain using a much lower pain stimulus than that needed for healthy controls[7-9]. Similar findings of diffuse hyperalgesia and allodynia, noted with both experimental pain testing and functional neuroimaging, are also found in a number of different CPSs, such as irritable bowel syndrome, interstitial cystitis, temporomandibular joint disorder, osteoarthritis[10].

These findings suggest that the similar pathophysiological mechanism in CNS play an essential role in a variety of CPSs, and that interventions by pharmacological or nonpharmacological measures of these pathological conditions may be effective for ameliorating these CPSs[11].

Pain facilitation mechanism related to CPS

Persistent, intense pain activates secondary mechanisms both at the periphery and within the central nervous system that cause allodynia, hyperalgesia, and hyperpathia that can diminish normal functioning[12]. These changes begin in the periphery with upregulation of cyclo-oxygenase-2 and interleukin-1β-sensitizing first-order neurons, which eventually sensitize second-order spinal neurons by activating N-methyl-d-aspartic acid (NMDA) channels and signaling microglia to alter neuronal cytoarchitecture[12-15]. Throughout these processes, prostaglandins, endocannabinoids, ion-specific channels, and scavenger cells all play a key role in the transformation of acute to chronic pain. A better understanding of the interplay among these substances will assist in the development of agents designed to ameliorate or reverse chronic pain[16].

Glutamate is known to act on NMDA receptors to

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produce increased pain "wind up" phenomenon of progressively increased central pain amplification after repeated painful stimulation, leading to greater hyperalgesia and allodynia[13,14].

Neuroimages of regional cerebral blood flow in areas of the brain associated with pain processing in patients with chronic pain show that patients with CPS exhibit changes in levels of neurochemicals and receptors associated with increased signaling in ascending pathways and decreased signaling in descending pain inhibitory pathways[17]. Increased levels of neurotransmitters in the cerebrospinal fluid (CSF) were also found in patients with CPSs.

Neurotransmitters that generally act to increase ascending input, including substance P, nerve growth factor, glutamate, other excitatory amino acids and brain-derived neurotrophic factor, have been shown to be elevated in both CSF and brain in patients with CPS such as fibromyalgia[18]. On the other hand, the activity of descending pain control pathways is also decreased, as indicated by lower CSF levels of metabolites of serotonin, norepinephrine, and dopamine[18,19]. By contrast, opioid levels are found to increase[19] with decreased opioid receptor binding[20], leading to that baseline endogenous opioidergic activity is increased in patients with CPS. The findings of decreased opioid receptor availability may explain why opioids are sometimes less effective in treating the fibromyalgia and other CPSs.

The disturbances of these neurotransmitters and neuroprocessing mechanisms also influence mood, energy, and sleep. Functions and imbalances of these neurotransmitters in different brain areas may help to explain, at least in part, the mood disorders, sleep dysfunction, and fatigue frequently associated with a variety of CPSs.

Important factors that may be associated with increased pain perception in CPS frequently include abnormal autonomic function, hypothalamic-pituitary-adrenal axis abnormalities[21], neurogenic inflammation[22], and neuronal loss[23].

Recent evidence presented by Aira et al.[24] implicates serotonergic descending facilitatory pathways from the brainstem to the spinal cord in the maintenance of pathologic pain. They reported that upregulation of the serotonin receptor 2A (5-HT(2A)R) in dorsal horn neurons promotes spinal hyperexcitation and impairs spinal μ-opioid mechanisms during neuropathic pain. Further, they found the involvement of spinal glutamate receptors, including metabotropic receptors (mGluRs) and NMDA, in 5-HT(2A)R-induced hyperexcitability after spinal nerve ligation (SNL), a model of neuropathic pain, in rat[24]. A role for 5-HT(2A)R is indicated in hyperexcitation and pain after nerve injury, and mGluR1 upregulation is supported as a novel feedforward activation mechanism contributing to 5-HT(2A)R-mediated facilitation[24].

In patients with CPS, the 2 main pain pathways may operate abnormally, resulting in central facilitation of pain signals[25,26]. The origin of this pain augmentation process might be multifactorial. Peripheral pain insults may have an initial role, but most current study suggests a strong role of CNS which becomes independent of peripheral nociceptive input. The result of both increased excitability of central neurons and reduced pain inhibitory mechanisms lead to symptoms of allodynia and/or hyperalgesia.

Other physiological processes varies tremendously between individuals which makes the CPS difficult to analyze. Central facilitation of pain sensation in the CPS is likely determined at least partially by genetics and modified by environmental factors[27,28].

Patients with CPS sometimes exhibit an increased sensitivity to a number of other sensory stimuli, including heat, cold, auditory, and electrical stimuli[17]. Pain is frequently accompanied by other, associated conditions, including irritable bowel syndrome, tension-type headache and migraine, temporomandibular disorder, chronic pelvic pain, vulvodynia, and interstitial cystitis, painful bladder syndrome, chronic prostatitis, and prostadynia[29,30].

Pain modulatory mechanism in patients with CPS

Pioneering study by Dr. Reynolds[31] in 1969 triggered the research on descending pain control system, endogenously existed in man and animals. He implanted the chronic monopolar electrodes in the region of the midbrain central gray in rats. In three of eight rats, continuous 60 cycle-per-second sine-wave stimulation resulted in an analgesia defined by the elimination of responses to aversive stimulation while general motor responsiveness was retained. He noted that electrodes

effective in inducing electrical analgesia at the lowest currents were located at the dorsolateral perimeter of the midbrain central gray. Thus, focal brain stimulation in this region can induce analgesia in the absence of diffusely applied "whole brain" stimulation[32].

During the same period, transcranial whole brain stimulation was also demonstrated to be effective for inducing surgical analgesia even in clinical setting[32]

On the other hand, Shealy et al.[33] implanted the first spinal cord stimulator device directly on the dorsal column for the treatment of chronic pain, based on the gate control theory. This technique, however, yielded various sequelae after the implantation. In 1971, Shimoji and colleagues first reported the analgesic properties of epidural spinal cord stimulation, based on the techniques of the continuous epidural analgesia[34]. Since then, this technique has undergone numerous technical and clinical developments.

Provoked by these studies, Kosterlitz' group[35] isolated two endogenous morphine-like substances:pentapeptides,methionine-enkephalin, H-Tyr-Gly-Gly-Phe-Met-OH and leucine-enkephaline,H-Tyr-Gly-Gly-Phe-Leu-OH from calf brain. Subsequently, Simatov and Snyder also isolated the two substances[36]. Several other endogenous opioid substances including beta endorphins were found in central nervous system in 1970's[37,38].

Owing to these discoveries, studies on descending pain inhibitory systems enlightened the researchers to work on endogenous modulation of pain.

In earlier studies, attention has been mainly focused on the descending inhibitory influence. Recently, however, it has also been known that the descending input from the RVM facilitates neuronal responses in the spinal dorsal horn and contributes to persistent pain and hyperalgesia as mentioned above[39,40]. Descending modulation is not a static process but exhibits dynamic changes in response to persistent noxious input following peripheral inflammation and nerve injury[41-45].

The descending pain modulatory system is thought to undergo plastic changes following peripheral tissue injury and exerts not only facilitatory but also inhibitory influences on spinal nociceptive transmission. The mitogen-activated protein kinases (MAP-Ks) superfamily consists of four main members: the extracellular signal-regulated protein kinase1/2 (ERK1/2), the c-Jun N-terminal kinases (JNKs), the p38 MAP-Ks, and the ERK5. MAP-Ks not only regulate cell proliferation and survival but also play important roles in synaptic plasticity and memory formation[46]. Many recent studies have demonstrated that noxious stimuli activate MAP-Ks in several brain regions that are components of descending pain modulatory system. They are involved in pain perception and pain-related emotional responses.

In addition, psychophysical stress also activates MAP-Ks in these brain structures. Thus, the convergence of mechanisms between noxious stimuli- and psychological stress-induced neuroplasticity is likely to occur in a variety of pain syndromes. A number of behavioral studies have suggested that the descending pain modulatory system is impaired in CPS with involvement of MAP-K[47].

Patients with fibromyalgia is found to display less connectivity within the pain inhibitory network in the brain during calibrated pressure pain, compared to healthy controls. It is possible that the dysfunction of the descending pain inhibitory structures and modulatory network between them plays an important role in maintenance of pain in CPS patients[48].

Structures responsible for descending pain modulation

(a) Cortex

The contralateral primary somatosensory cortex (SI) is known to be activated during pain[49], but the ipsilateral SI is shown to be deactivated[11,12]. In addition, interactions between SI and cerebral subregions during maintained nociceptive stimulation are shown to be accompanied by an altered SI response to myelinated and unmyelinated nociceptors[50]. During manipulation analgesia, SI is more deactivated than during pain or nonpainful state[12]. The finding of an SI deactivation during manipulation analgesia suggests that this region may be actively inhibited during activated analgesia by manipulation.

Regions such as the dorsolateral prefrontal cortex (DLPFC), middle cerebral cortex (MCC), and insular cortex exhibits significantly greater activity during manipulation analgesia than during pain, and thus, could be involved in the generation or maintenance of manipulation analgesia in man[50]. The DLPFC has connections with the PAG in humans[51,52] and electrical

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stimulation of the prefrontal cortex can produce antinociception in animals[53]. This analgesia is blocked by pretreatment with naloxone, a μ-opioid antagonist, suggesting that left DLPFC drives top-down opioidergic systems[54,55].

The MCC has frequently been reported to participate in pain processing and attention[56]. It has also been shown that he MCC exhibits increased activity during hypnotic suggestions for analgesia as well as opioid analgesia[57]. Pain relief was reported in phantom limb pain[58] and post-stroke pain[59] by electrical stimulation of motor cortex in human.

Epidural or transcranial motor cortex stimulation (MCS), magnetic or electrical, has been proposed as a treatment for chronic, drug-resistant neuropathic pain of various origins. The indication of MCS might be extended to various types of refractory, chronic peripheral pain beyond trigeminal neuropathic pain[60-66].

The insular cortex receives input from the thalamus, amygdala, and also SII 67. The insula is commonly thought to play a role in integrating sensory information with its emotional context 68 and interceptive awareness 69, and can be involved in pain modulation[67-72].

The activation of MAPKs including ERK1/2, JNK, and p38 MAPK has been shown to be critical for induction of long term potentiation (LTP) in the anterior cingulate cortex (ACC)[73]. ERK1/2 activation in the rACC seems to be critical for the development of affective pain (pain-related emotional response) but not nociceptive pain[74].

ERK1/2 activity in the PFC may be critical to depressive-like behavior and memory impairment. The rats subjected to prenatal stress showed a decrease of p38 MAPK activation in the PFC[75]. In these stressed rats, protein phosphatase-2A that dephosphorylates all MAPKs has been found to increase in the PFC. It has also been reported that p38 MAPK activation is involved in long-term depression (LTD) at excitatory synapses of PFC pyramidal neurons[76]. These stress-induced reductions of MAPKs activation may impair synaptic plasticity. On the other hand, it is speculated that chronic pain stress-induced ERK1/2 activation could cause neuronal atrophy and reorganization, since sustained activation of MAPK induces neuronal degeneration[77-79].

(A) Amygdala

The amygdala is now believed to be an important player in the emotional-affective behavior of pain[80,81]. It has also been demonstrated that this structure modulates nociceptive behavior by affecting the activity of rostral ventromedial medulla (RVM)[82,83].

Recently, it has also been shown in human individuals that the drug-induced reduction in the unpleasantness of hyperalgesia is positively correlated with right amygdala activity. A naturally occurring cannabinoid,delta-9-tetrahydrocannabinol (THC), may reduce functional connectivity between the amygdala and primary sensorimotor areas during the chronic pain state. It is suggested that dissociative effects of THC in the brain are relevant to pain relief in humans[84].

The interesting hypothesis has just been proposed that the amygdala is a relay station for switching on and off pain, composing a potential hot spot in supraspinal descending pain control. According to this hypothesis, upon pain stimuli, corticotrophin-releasing factor type 1 receptor (CRFR1) in the amygdala is activated by CRF to induce hyperalgesia. When the activated CRFR1 is internalized (pain initiation), it triggers the translocation of the cytoplasmic CRF type 2 receptor (CRFR2) to the plasma membrane. Here, CRFR2 can be recruited by either high concentrations of CRF or by endogenous CRFR2 ligands, the urocortins, leading to analgesia (pain termination).

This on-off switching of pain is completed by redistribution of the CRF receptors to their initial activity state. Rouwette et al[85] also propose that in neuropathic pain, this mechanism is deregulated and causes a state of permanent hyperalgesia, and present an integrative pathophysiological model for the way disturbed CRF receptor signaling in the amygdala could initiate neuropathic pain.

The amygdala including basal ganglia (BG) have been implicated in different processes that control action such as the control of movement parameters but also in processing cognitive and emotional information from the environment. The BG form a system that is fairly different from the limbic system, but have strong ties, both anatomical and functional, to the latter. Different models for their functions for pain processing have still been proposed[86,87].

Ugawa[4] describes the two systems contributing

to pain signs in patients with basal ganglia disorders. Descending pain modulation system: several brainstem nuclei send descending pain modulation fibers to the spinal cord mediated by serotonin or noradrenalin. These nuclei are facilitated by dopamine D2 neurons from the striatum. Striatal dopamine must suppress the pain information input at the spinal cord. Ascending pain relief system: D2 neurons from the ventral tegmental area to anterior cingulate cortex, accumbens and amygdala may reduce pain feeling at the association cortices. Dopamine depletion, therefore, will enhance the pain sensation.

Amygdala-driven abnormal inhibition and decreased output of medial prefrontal cortex (MPFC) pyramidal cells is shown to contribute to pain-related impaired decision-making[87].

In addition, human patient studies suggest reduced hippocampal volume and function in elderly individuals with chronic pain[88].

It has been shown that ERK1/2 activation in the amygdala plays a pivotal role in inflammation-induced mechanical hypersensitivity. ERK1/2 activation mediates plasticity in various brain regions. Furthermore, it has been demonstrated that ERK1/2 activation in the central nucleus of the amygdala (CeLC) is downstream of metabotropic glutamate receptor 5 (mGluR5)[89]. The level of mGluR5 in the right amygdala was higher than that in the left amygdala. This seems to be one of the mechanisms for hemispheric lateralization of pain processing in the amygdala. On the other hand, MAPK activation in the amygdala seems to be implicated in the formation of depressive-like behavior[90,91]

(B) Hippocampus

It is common clinical experience that anxiety about pain can exacerbate the pain sensation. The report by Ploghaus et al[92] using fMRI in human supports the proposal that during anxiety, the hippocampal formation amplifies aversive events to prime behavioral responses that are adaptive to the worst possible outcome.

The findings by Gondo et al[93] also indicate that anxiety's alteration of the network that includes the hippocampus and that is associated with pain modulation underlies the manifestation of somatization, in which individual daily physical symptoms were assessed by using the somatization subscale of the Symptom Checklist 90 revised (SCL-90-R).

On the other hand, chronic neuropathic pain-like behavior in the rats correlates with IL-1β expression and disrupts cytokine interactions in the hippocampus[94].

This cytokine is also overexpressed at supraspinal brain regions, in particular in the contralateral side of the hippocampus and prefrontal cortex and in the brainstem, in rats with neuropathic pain-like behavior[95]. Neuroimaging studies, however, have shown that no clearly defined "pain centre" exists. Rather, an entire network of brain regions is involved in the processing of nociceptive information, which leads to the subjective impression of "pain"[96].

Melzack[97,98] proposed that the brain possesses a neural network—the body-self neuromatrix—which integrates multiple inputs to produce the output pattern that evokes pain. The body-self neuromatrix comprises a widely distributed neural network that includes parallel somatosensory, limbic and thalamocortical components that subserve the sensory-discriminative, affective-motivational and evaluative-cognitive dimensions of pain experience. The synaptic architecture of the neuromatrix is determined by genetic and sensory influences. Thus, he presented a theoretical framework in which a genetically determined template for the body-self is modulated by the powerful stress system and the cognitive functions of the brain, in addition to the traditional sensory inputs. This concept of "neuromatrix" for pain is well supported[99].

Recent data by Gao et al.[100] suggest that the analgesic effect of electroacupuncture is mediated by regulation of hippocampal proteins related to amino acid metabolism and activation of the MAPK signaling pathway.

Hippocampal CA1 area may also be involved in opioid-induced analgesia and naloxone-induced nociception through nitric oxide biosynthesis[101,102].

Long-term changes in histone H3 phosphorylation by pain and stress have recently been reveled in rat hippocampal CA3 neurons, which depend on genetically determined functional status of the nervous system.

Chronic pain crucially influences hippocampal plasticity related to cognitive function. Increasing the extracellular level of glycine via blockade of the selective glycine transporter 1(GlyT1) may be one of the thera-

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peutic approaches for chronic pain with memory impairment[103]

(b) Other cortices

Other regions of the cortex are shown to be deactivated during manipulation analgesia[12]. The precuneus and medial prefrontal cortex are deactivated during both pain and manipulation analgesia[12]. The medial prefrontal cortex (MPFC) and the precuneus that show the highest resting metabolic rates in the brain during rest[103] are commonly deactivated during sensory and attention related tasks. The dorsal MPFC is found to be more deactivated during manipulation analgesia than during rest or pain[12].

MPFC is also suggested to contribute to introspective-oriented mental activity[104] and left to be studied for its concrete role in pain inhibition.

(c) Thalamus

Several regions in the ventrobasal thalamus (VPL) are shown to be activated during pain with differences in indivisual neurons[105] but most activated during inhibitory manipulation[12]. These regions are known to receive afferent nociceptive input.

Findings in animals indicate that the spinothalamic tract carries nociceptive information to several target nuclei within the posterior thalamus, leading to the evidence that this projection provides nociceptive information that plays an important role in pain perception[106-108].

A toxin has been developed (SSP saporin) that binds to the substance P receptor of nociceptive neurons, and interesting data have been reported by Ralston that the SSP-saporin administration to the lumbar spinal cord destroys a relatively small number of the total neurons that project into the somatosensory thalamus and does not lead to demonstrable changes in the inhibitory circuitry of the thalamus, in contrast to lesions of major pathways that lead to reductions in the thalamic inhibitory circuitry[109].

On the other hand, stimulation of the VPL and VPM produces analgesia in patients with chronic pain[110], and has been shown to inhibit spinothalamic tract neurons in animals[111]. The activation of inhibitory interneurons in thalamus may show feed forward projections from PAG to thalamus[111].

The results in the experimental chronic constriction injury (CCI), a model of chronic neuropathic pain, suggest that CCI induced a region-specific adaptation of μ-opioid receptor-mediated G-protein activity, with apparent desensitization of the μ-opioid receptor in the thalamus and PAG, which means reduction of μ-opioid receptor-mediated G-protein activity in these regions[112].

On the other hand, the data of Seminowics et al[113] suggest that below-level hypersensitivity by spinal cord injury is associated with functional disconnection (asynchrony) between the thalamus and cortical areas involved in nociceptive processing.

(d) Hypothalamus

The study by Liebeskind group in rats indicates that the hypothalamic paraventricular nucleus (PVN) is part of the brain's pain inhibitory system, and shows that the analgesia induced by electrical stimulation of PVN is not mediated by either vasopressin or opioid peptides[114].

On the other hand, PVN morphine injection is reported to cause significantly longer paw lick latency (PLL) than the control in both normal and hypophysectomized rats. The analgesia induced by PVN morphine injection was not affected by hypophysectomy[115].

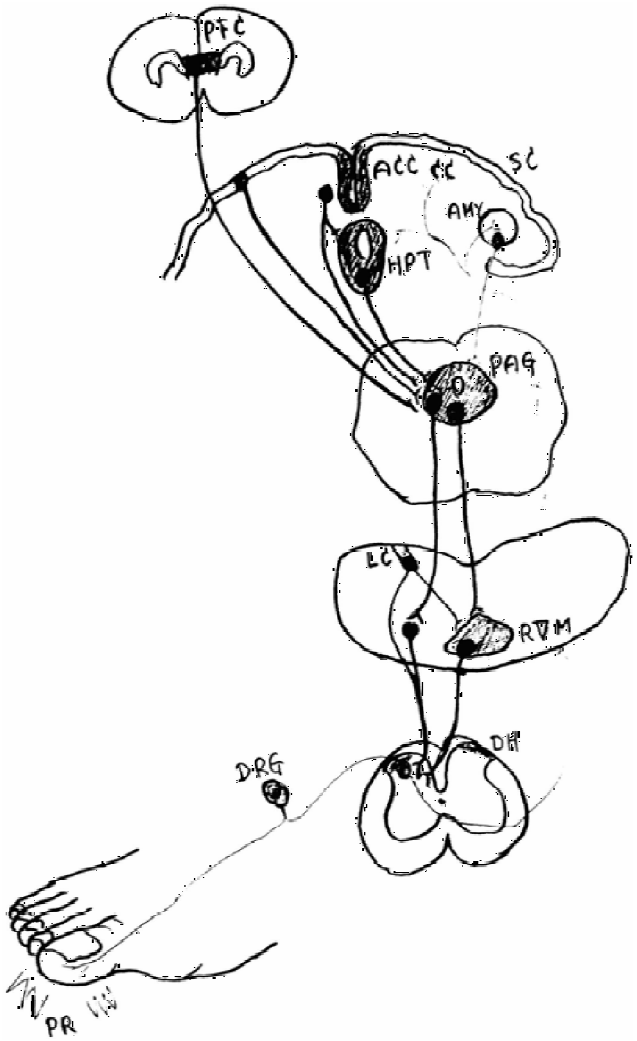
Further, intracranial self-stimulation (ICSS) of the PVN of the hypothalamus in the rat is facilitated to a greater extent by morphine than cocaine, and unaltered after spinal nerve ligation. The PVN may have a greater role in the reinforcing effects of opioids than classic limbic regions, particularly in the presence of chronic pain[116].

The hypothalamus is also considered to be involved in cluster headache which is the most common type of trigemino-autonomic headache. The attacks of pain related to cluster headache are accompanied by trigemino-autonomic manifestations and restlessness. The attacks often possess a circadian and seasonal rhythm[117].

Posterior inferior hypothalamic stimulation is now established as a treatment for many chronic cluster headache patients. The technique is shedding further light on the pathophysiology of the disease, and is also providing clues to functioning of the hypothalamus itself[118].

Beta-endorphin neurons in the hypothalamic arcuate (infundibular) nucleus (Arc) project to the PAG

and activate descending projection neurons to the RVM in the PAG by inhibiting inhibitory GABA-ergic interneurons. This neural circuit has been implicated in the production of stimulation-produced and stress-induced analgesia[119-121] (Figure 1). An inflammatory pain model, formalin injection into the hindpaw, activated ERK1/2 in the hypothalamus[122]. ERK1/2 activation markedly increased at 30min and remained higher than baseline after 24h. p-ERK1/2 was colocalized with beta-endorphin in the Arc neurons. Proopiomelanocortin (POMC) is a precursor to several active peptides, including beta-endorphin[122].



Thick lines represent the descending fibers, and the fine lines the ascending fibers. FPC, prefrontal cortex; ACC, anterior cingulate cortex; AMY, amyglala; HPT, hypothalamus; PAG, periaqueductal gray; LC, locus coeruleus; RVM, rostral ventromedial medulla; DH, dorsal horn; DRG, dorsal root ganglion; PR, pain receptor

Figure 1 : Schematic drawing of pain modulation at several different central nervous structures.

The i.c.v. injection of PD98059 attenuated formalin-induced increase of POMC mRNA expression in the hypothalamus. These results indicate that ERK1/2 activation in the hypothalamus may contribute to neuroendocrine regulation[122]. ERK1/2 activation in the hypothalamic PVN has also been reported after intraplantar formalin or intrathecal SP injections[123,124]. The i.c.v. injection of an MEK1/2 inhibitor, PD98059, attenuated the second phase of formalin-induced nociceptive behavior[124]. Therefore, ERK1/2 activation in the PVN may be involved in nociceptive behavior. These activations in the Arc and the PVN might be involved in autonomic and endocrine responses to the pain stress. Those functions remain elusive, however.

Prostaglandin (PG) D(2), the most abundant PG in the central nervous system (CNS), particularly in the hypothalamus, is a bioactive lipid having various central actions including sleep induction, hypothermia and modulation of the pain response[125].

(e) Periaqueductal gray matter (PAG)

The PAG and related brainstem regions has been found to be important in pain inhibition. These regions are transiently activated during pain reduction by an intervention (offset analgesia)[8]. The inhibitory effect of PAG manipulation With such dynamic activation, their capacity for pain control can be utilized for the temporal 'filtering' of nociceptive information[8].

The activation within the PAG may be the most physiologically significant among the supraspinal regions. The PAG is more active during manipulation analgesia than during pain without manipulation. The activation is found in the ventral PAG and extended laterally[8]. When this region of the PAG is electrically stimulated in patients with intractable pain, patients report analgesia and even a feeling of "well-being"[126].

Electrical and pharmacological activation of the PAG can cause antinociception and analgesia in animals and humans, respectively[127,128]. The ventrolateral PAG receives both the afferent input and efferent output required for pain inhibitory activity. Afferent input that drives neuronal activity within the PAG projects from the prefrontal cortex, amygdala, numerous medullary and pontine nuclei, including both serotonergic (nucleus raphe magnus, NRM; nucleus paragigantocellularis, NRPG; nucleus tractus solitarius,

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NTS), and noradrenergic (locus cellureus, LC; parabrachialis,PB; Kölliker Füse nucleus, KF) nuclei, as well as spinal structures[129-131].

The PAG's efferent connections are thought to be most important for centrifugal control of pain. The PAG also projects directly to every level of the spinal cord[132-137]. The PAG projects to other brainstem nuclei (NRM, NRPG, LC, PB, and NTS), to the thalamus, and to cortical regions involved in pain mechanism[136-138]. Thus, the ventrolateral PAG has both the afferent and efferent projections for pain control mechanisms.

ERK1/2 is reported to be activated in several PAG neurons related to the different functional activity such as fear, anxiety, defensive reactions, and autonomic regulation in response to nociceptive stimuli[139].

(f) Brain stem nuclei

The regions in brainstem, the midbrain, thalamus, and cortex are known to be involved in nociceptive processing. In addition, the brainstem activations are found to be highly focal and does not exhibit a distinct spatial distribution. Functional correlation of the PAG with brainstem nuclei reveals focal and discrete.

The areas of discrete activation are consistent with both serotonergic (nucleus raphe magnus,NRM; dorsal raphe nucleus, lateral reticular nucleus, DRN; nucleus tractus solitaries,NTS) and noradrenergic (locus culleus,LC; nucleus parabrachialis, PB ; Kölliker Füse nucleus,KF ; A1 and A5 cell groups in the caudal portion of the ventrolateral medulla) nuclei[140,141]. Each of these nuclei shows very complex circuitry with complex reciprocal interconnections to other nuclei involved in pain modulation[140,142-144]. Recent study has also shown that patients with fibromyalgia display less connectivity among these nuclei in pain inhibitory network[145]

Each of these regions has been shown to produce analgesia when stimulated and has either direct or indirect output to the spinal cord[140,142-144] and therefore could potentially participate in the pain inhibition in terms of its time course and magnitude[145].

(A) RVM (Rostral ventromedial medulla)

The RVM has been known as the structure to send its inhibitory activities to the neurons in the spinal cord responsible for sending pain impulses to the brain.

Recently, however, by depleting endogenous 5HT in the RVM serotonergic neurons, it has been demonstrated that the RVM 5HT system participates in descending pain facilitation but not descending inhibition, which is necessary for maintenance of hyperalgesia and allodynia after peripheral inflammation and nerve injury[146]. The 5HT receptor subtypes,5HT1A receptors, are shown to be involved in the effects of morphine in the shock titration procedure, whereas 5HT2, 5HT3 and alpha 2 adrenergic receptors do not appear to play a role in morphine's effects in squirrel monkeys[147].

Oyama et al.[148] reported that the inhibitory and facilitatory effects were mediated by 5HT1A and 5HT3 receptors, respectively, in the rat spinal cord. Nearly one-half of DRG neurons projecting to the superficial dorsal horn express 5HT3 receptor[149], and activation of 5HT3 receptor localized on central terminals of DRG neurons seems to enhance the release of neuropeptides[150].

(B) Locus coeruleus (LC)

The coeruleospinal inhibitory pathway (CSIP), the descending pathway from the nucleus locus coeruleus (LC) and the nucleus subcoeruleus (SC), is one of the centrifugal pain control systems and suggested to suppress pain system to extract other sensory information such as acoustic startle simulation[151] that is essential for circumstantial judgment[152].

A disturbance in hemilateral pain processing that involves the locus coeruleus could exacerbate the symptoms of CRPS in some patients[153].

Several studies have demonstrated that acute restraint stress increases p-ERK1/2 in the LC[154,155–157]. On the other hand, chronic restraint stress induced further marked activation of ERK1/2, JNK, and p38 MAPK in the LC[155]. ERK1/2 activation in the CeLC neuron also contributes to synaptic facilitation by increasing NMDA receptor function after peripheral inflammation[154].

Other study has reported that induction of tyrosine hydroxylase in the LC of transgenic mice in response to stress or nicotine treatment does not activate tyrosine hydroxylase promoter activity[158].

The disparity among those experimental results may be due to the differences in duration of restraint stress and experimental protocol. LC neurons in waking ani-

mals are very responsive to nonnoxious auditory, visual, and somatosensory stimuli in the environment[159–162]. Thus, experimental environment must be taken to account to evaluate an activation of MAPK in the LC.

(g) Spinal cord and feedback inhibition

Numerous studies have been carried out in the spinal cord of animals and man as the primary site of pain modulation, particularly since the gate control theory by Melzack and Wall. Cumulative data show that the spinal cord plays an important role for the first common pathway to send the pain information to the supraspinal nuclei which integrate the various neuronal impulses into feedback modulatory outputs.

Particularly, interest have been focused on the dorsal horn lamina II or the substantia gelatinosa (SG), which is recognized as the key nucleus in the spinal cord for controlling the pain information from the periphery to the brain[163-171]. Recent studies have shown that not only the chemical changes but plastic changes occur in the SG and even primary sensory neurons in chronic pain[172-174]. The plastic changes may originate from structural changes of neurons and surrounding tissues[175-178]. Even in neurons, these changes may occur not only in the synaptic but also in extrasynaptic receptors in CPS[179].

It is well known that spinal cord stimulation (SCS) and even peripheral nerve stimulation (PNS) provoke the central nuclei responsible for descending inhibition to send back the inhibitory impulses on pain pathways[180,181]. Clinical studies have shown that spinal or cerebral neurostimulation can significantly relieve pain. Even a closed-loop feedback system has been developed in configuration, thereby suppressing excessive activity in spinal cord dorsal horn neurons[182].

However, the precise mechanisms of this feedback inhibition are still left to be investigated.

Besson and Rivot[183] first identified the interneurons presenting heterotopic and heterosensory convergence in laminae VI-VII of the lumbar dorsal horn in the cat. They showed that stimulation of the hind limbs sometimes induced a bimodal response, but only the late convergent discharge.

Response latencies are longer to hind limb than to forelimb stimulation at this level suggesting the intervention of a supraspinal loop in the activation of spinal convergent units. This hypothesis is supported by the relationship between the excitability of supraspinal structures and the discharge intensity of convergent cells as well as by the absence of long latency responses in the spinal preparation and even in human[184-186]. Electrophysiological and pharmacological evidence discloses a strong relationship between convergent unit discharges and the occurrence of dorsal root potentials to cortical, heterosegmental and heterosensory stimulations[187,188].

It is suggested that convergent neurons receive information of supraspinal origin and exert control over sensory input to the cord via primary afferent depolarization[188]. Since the work by Besson's group there have been few studies on heterosegmentally activated feedback inhibition except the reports on rats and human by Shimoji' group[189-191].

CONCLUSION

Generally, it is believed that the pain pathway consists of three neurons: the primary nociceptive, spinothalamic, and thalamo-cortical neurons. The third neuron terminates in the cerebral cortex where pain is perceived. While this simple anatomic structure is useful for diagnostic purposes in some patients, the clinical symptoms are difficult to analyze in most patients with CPS. For instance, when nociception occurs in the periphery, pain is not restricted to the levels of thalamus and the cortex.

Pain results from interactions of excitation and inhibition of not only these classical pathway but also from divergence and convergence of other CNS structures as described. In addition to the intrinsic pain inhibitory or antinociceptive structures such as the periaqueductal gray matter and the brainstem nuclei, roles of several recently discovered members of the antinociceptive system are added, such as the pretectal nucleus, the reticular formation, the nucleus accumbens, the nucleus tractus solitarii, the reticular thalamic nucleus, and other areas.

The localisation of cortical and deep brain neurons involved in the generation of pain as well as inhibition of pain have recently been presented by means of imaging techniques in human, and have started to be applied in clinical setting. Pain modulation should be targeted at various levels where pharmacological or non pharmacological intervention may be carried out effectively.

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