# Pathophysiology of Chronic Daily Headache

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Despite no clear explanation of the mechanism underlying chronic daily headache, sensitization of central nociceptive neurons is one possibility. Either prolonged activation of peripheral nociceptors or any factors that can alter the endogenous pain control system can trigger this process. A decrease in platelet serotonin has been observed in patients with chronic tension-type headache as well as migraine patients with medication-induced headache. It was also shown that chronic analgesic exposure led to changes in the serotonin content and the density of the 5-$HT_{2A}$ receptor in the cerebral cortex. The plasticity of the serotonin-dependent pain control system may facilitate the process of sensitization and results in the development of chronic daily headache.

## Introduction

The chronic daily headache (CDH) is characterized by the daily or almost-daily occurrence of headache. Its pattern is usually episodic in the beginning, either in the form of migraine or tension-type headache. In some cases the headache can be daily ab initio. According to the temporal courses and patterns, this syndrome can be classified into four categories, including transformed migraine, chronic tension-type headache, new daily persistent headache, and hemicrania continua [1]. The varieties of its natural history and clinical presentations also imply the heterogeneity of this syndrome.

No clear explanation exists regarding the pathogenesis of headache transformation. Despite its clinical varieties, the development of daily headache from an initial episodic character, either migraine or tension-type headache, may share some common mechanisms. Various factors, including overuse of analgesics, associated psychiatric disorders, chronobiological factors, and so forth, have been proposed to be accounted for this process. This article reviews the biological changes observed in the patient with CDH. The possible mechanism underlying the process of headache transformation is also proposed. Special attention is paid to the possible pathogenesis of analgesics abuse headache.

## The Clinical Standpoint

Chronic daily headache and its episodic counterpart differ both in frequency and headache characters. Comparison between migraine and transformed variants, headache in the latter, tends to be more bilateral and persistent dull pressure-like in nature [2]. These characters resemble the headaches observed in chronic tension-type headache than those of migraine. Cutaneous allodynia, in the form of scalp tenderness, is frequently observed. The associated symptoms such as nausea, vomiting, photophobia, and so forth appear not very often. The recent survey showed the significant associated factors of this headache to be analgesic overuse, history of migraine, and depressive mood [3]. Sleep difficulties are also a common symptom, which coincides with the daily headache. Recently, Spierings *et al.* [4] showed that daily headaches did not differ in their features regardless of whether the initial headaches were migraine or tension-type headache. They also showed that when daily headache became intermittent again, it reassumed the features of initial headache.

These clinical presentations may offer some clues for the possible mechanisms underlying the process of headache transformation. Decreased pulsating pain may reflect the changes in the primary organ of the headache generator from cranial vessels. Spreading of the headache area and cutaneous allodynia may indicate the change in the receptive field and sensitivity of the central nociceptive neurons. The similarities in the daily headache characters, regardless of the types of initial headache, might imply that the process of transformation finally results in the common pathophysiologic state. It is known that serotonin (5-hydroxytryptamine [5-HT]) plays an important role in the pathogenesis of depressive disorder and sleep disturbance. Therefore, coexistence of these associated psychiatric symptoms may indicate the role of a certain neurotransmitter, particularly 5-HT, in this process.

## Sensitization and Pathogenesis of Chronic Daily Headache

Pathophysiologic processes underlying CDH can be classified, according to the pain generators, into peripheral and central mechanisms. The peripheral mechanism is related to the changes in nociceptor function, especially those innervating the cranial vessels and pericranial myofascial tissues. The central mechanisms comprise physiologic changes in the neural pathway, subserving the transmission and modulation of cranial nociceptive information.

### Peripheral mechanisms

Activation of the trigeminal nerve is known to be the final common pathway of all forms of headache. Perivascular and pericranial myofascial nociceptors exert an important role in the generation of headache in migraine and tension-type headache, respectively. The activation of nociceptive fibers then triggers the release of algogenic peptides, including substance P and calcitonin gene-related peptide (CGRP), from its terminals. The released mediators can induce mast cell activation, nociceptor sensitization, and perivascular protein extravasation. Coupling of these ligands with their receptors, mainly G protein-coupled subtype, can then trigger phosphorylation of various proteins, including ion channels. Phosphorylation of sensory neuron-specific tetrodotoxin-resistant sodium channels as well as calcium channels will decrease the threshold of the nociceptor membrane (Fig. 1). As a result, the nociceptor becomes more ready to fire and some inactive or "silent" nociceptors are turned on. This process is known as peripheral sensitization. Sensitization of perivascular nociceptors is possibly responsible for the development of the pulsating headache developed during the migraine attacks. Repeated episodes of trigeminal nerve activation may chronically sensitize nociceptors and thus contribute to the development of CDH.

Although the nociceptor sensitization seems to explain the pathogenesis of CDH, lack of definite evidence renders this as a speculation. Concerning chronic tension-type headache, Sakai *et al.* [5] found that patients with chronic tension-type headache had a higher degree of trapezius muscle hardness than the controls. More recently, a significant relationship between hardness and tenderness of the trapezius muscle was demonstrated in the patients suffering from this condition [6]. Because there is no difference in hardness recorded on days with and days without headache, such an increase in muscle hardness is unlikely to be a consequence of actual pain. These findings may reflect an increase in the sensitivity of nociceptors distributed in the pericranial muscles. The possible beneficial effect of botulinum toxin injection in the treatment of migraine as well as its transformed variants also indicates the role of muscle nociceptors in the process [7–9]. The exact mechanism inducing this peripheral sensitization is still unknown.

The evidence of peripheral sensitization in CDH patients, other than chronic tension-type headache, is still lacking. Change in the peripheral nervous system reported so far is the autonomic dysfunction. In 1998, Evers *et al.* [10] studied the peripheral sympathetic activity in headache patients by measuring the peripheral autonomous potential (PAP). They observed that patients with headache of any type had longer latency of PAP. This observation seemed to be specific for only headache because it was not observed in patients with low back pain. They also found that patients with medication-induced headache had increased PAP latencies compared to those with other forms of headache. Based on this observation, they concluded that sympathetic hypofunction as evidenced by prolonged PAP latencies is a general phenomenon in headache, and drug abuse may lead to an exaggeration of this phenomenon. The clinical significance of this finding is unclear.

### Central mechanisms

Any processes leading to an increased excitability of neurons in the central nociceptive pathway can be responsible for the development of chronic pain syndromes including headaches. At the level of the spinal dorsal horn neuron, its excitability depends on the input from primary afferent as well as segmental and supraspinal pain-modulating circuits. One important feature of synaptic transmission between primary nociceptive afferents and dorsal horn neurons that underlies the plasticity of dorsal horn neurons is the complexity of its neurotransmitter system. Central terminals of C-fiber neurons contain multiple transmitters including glutamate and the peptides, substance P, and CGRP. Various forms of receptors, both ionotropic and metabotropic types, are expressed on the cell membrane of postsynaptic dorsal horn and trigeminal nucleus caudalis neurons. The combination of these chemical reactions elicits long-lasting synaptic potentials. This slow synaptic potential promotes temporal summation and is responsible for the development of a physiologic phenomenon known as "wind-up." This phenomenon was described as progressively increasing activity in dorsal horn cells following repetitive activation of primary afferent C-fibers. This response is nonlinear and activity-dependent. The nonlinear nature of this increment can be explained by the recruitment of *N*-methyl-D-aspartate (NMDA) receptors through the removal of voltage-dependent blockade by magnesium ions. Activation of the NMDA receptor as well as other metabotropic receptors, *eg*, neurokinin-1 receptor, results in an increase in the intracellular calcium in the postsynaptic neurons. The rising of intracellular calcium will lead to substantial changes in the postsynaptic function. The increased calcium will activate nitric oxide synthase and increase the production of nitric oxide. This gaseous molecule then diffuses back to the presynaptic terminals and stimulates transmitter release (Fig. 2), which results in the long-term strengthening of the synaptic function and leads to the development of central sensitization. Central sensitization is both induced and maintained in a transcription-independent manner.

Several different intracellular signal transduction cascades converge on mitogen-activated protein kinase

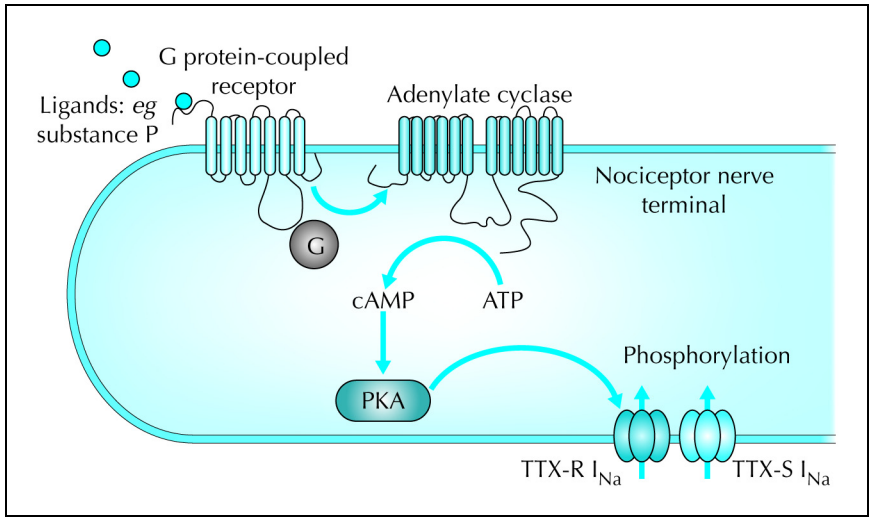


**Figure 1.** Biochemical pathway underlying the sensitization of the peripheral nociceptor. Various mediators released from injured tissues, circulating cells, and activated nociceptors will interact with their receptors, mainly the G protein-coupled subtype. cAMP—cyclic AMP; PKA—cAMP-dependent protein kinase; TTX-R $I_{Na}$–tetrodotoxin-resistant sodium channel; TTX-S $I_{Na}$–tetrodotoxin-sensitive sodium channel.

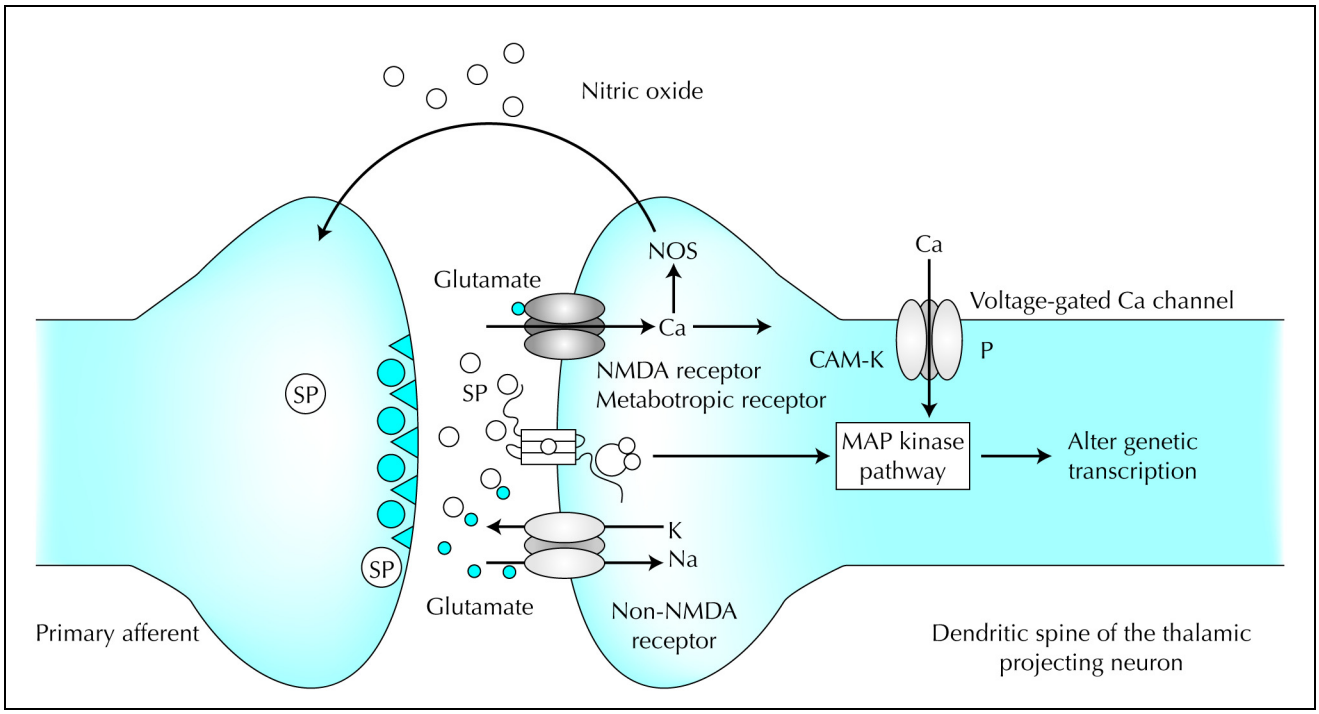


**Figure 2.** Synaptic mechanism underlying wind-up and central sensitization. Prolonged and repetitive activation of primary afferent fibers can trigger the release of glutamate and algogenic peptide, *ie*, substance P (SP). The slow synaptic potential promotes temporal summation and is responsible for the development of wind-up. Activation of the *N*-methyl-D-aspartate (NMDA) receptor results in an increase in the intracellular calcium; the increased calcium will activate nitric oxide synthase (NOS) and increase the production of nitric oxide. This gaseous molecule then diffuses back to the presynaptic terminals and stimulates transmitter release, resulting in the long-term strengthening of the synaptic function and leading to the development of central sensitization. Activation of the G protein-coupled receptor as well as an increase in cellular calcium can trigger several kinase systems, thus altering the genetic transcription. CAM-K—Ca2+/calmodulin-dependent protein kinase; MAP—mitogen-activated protein.

(MAPK), the activation of which appears to be a master switch or gate for the regulation of central sensitization. In addition to post-translational regulation, the MAPK pathway may also regulate long-term pain hypersensitivity, via transcriptional regulation of key gene products [11•]. As a result of sensitization, these central nociceptive neurons will become responsive to low-intensity stimuli as well as increase their responses to suprathreshold stimuli. These functional changes underlie the allodynia and hyperalgesia observed in the patients with chronic pain as well as chronic headache. The process of central sensitization also enlarges the receptive fields of these neurons, thus expanding the pain area. Burstein *et al.* [12] demonstrated that sensitized trigeminal caudalis neurons initiated by chemical stimulation of the intracranial dura showed an increased response to facial stimulation. Unlike the wind-up, central sensitization does not depend on the activity of primary afferents.

The induction of peripheral and central sensitization has been proposed to be significant steps in the development of headache and allodynia in migraine patients. In 2000, Burstein *et al.* [13••,14,15] described the temporal pattern of cutaneous allodynia developed during the migrainous attack. The mechanical and cold allodynia progressed from the ipsilateral head to the contralateral side and finally involved the forearm area. Based on this temporal profile, they proposed that the chemical activation of dural nociceptors developed during the migrainous attack could lead to the peripheral sensitization of these nociceptors to intracranial mechanical stimulation. The barrage of impulses that comes from peripheral nociceptor activates the second-order neurons and initiates their sensitization. Consequently, the barrage of impulses from the sensitized second-order neurons activates and eventually sensitizes third-order neurons. These findings provide the evidence for the induction of peripheral and central sensitization along trigeminovascular pain pathways by visceral input from the intracranial dura. They also explain the roles of peripheral and central sensitization in the development of throbbing pain in migraine and scalp tenderness, respectively. Abnormal sensitization has also been proposed to underlie the development of pain in various conditions including chronic tension-type headache [16••] and fibromyalgia [17]. Chronic activation of the intracranial nociceptors may enhance these processes and result in CDH.

## Neurophysiologic Evidences Supporting Central Mechanism

Changes in psychophysical measures supporting the sensitization theory have been reported in headache patients. Lowering in the pain threshold after prolonged heat stimulation in headache patients implied the sensitization in the spinal level [18]. Abnormal pericranial tenderness was also demonstrated in patients with CDH. Alteration of central excitation circuits has been proposed in these patients. Fusco *et al.* [19] demonstrated that the temporal summation of the second pain, the psychophysical correlate of the excitatory pain circuits, was greater in these patients in comparison with patients with migraine or episodic tension-type headache. They also showed that this facilitation could be normalized after drug discontinuation.

Over-consumption of analgesics, the factor related to the development of CDH, is also associated with changes in some electrophysiologic parameters. Using the critical flicker frequency (CFF) analysis, Schnider *et al.* [20,21] showed that the vigilance or attentive system was impaired in the patients with analgesic abuse headache. They also demonstrated that the decreased CFF value became normalized after analgesic withdrawal. Evers *et al.* [22] showed that the ergotamine abuse could affect information processing as evidenced by an increase in P3 latency of the event-related potential compared with migraine patients. However, whether or not patients with CDH have impairment in certain cognitive functions is still a question. A more recent study showed that the difference in CFF value disappeared after correction for total SCL-90 scores, a psychological measure [23]. This finding implies that ergotamine abuse is associated with psychological distress but not with structural impaired cognitive functioning.

Contingent negative variation (CNV) is the surface negative slow potential elicited in expectancy conditions. An increased negativity of the early and late component of this electrophysiologic phenomenon due to reduced habituation has been observed in migraine patients [24]. This phenomenon can be interpreted as an enhanced self-regulatory mechanism necessary for migraine patients to cope with the possible genetic cortical hypersensitivity. Change in this electrophysiologic characteristic has been observed in migraine patients with superimposed CDH. In 1998, Siniatchkin *et al.* [25] demonstrated the reduction of the negativity of the late component and pronounced postimperative negative variation in migraine patients who eventually developed CDH. Because the amplitude of the negativity of CNV has been proposed to reflect the degree of the self-regulatory mechanism, the observed reduction might indicate a loss of this compensatory mechanism in CDH. It should be noted that the same pattern of CNV abnormality could also be observed in the patients with depression, a major comorbidity of CDH.

## Dysfunction of Central Serotonin System As a Mechanism of Analgesic-induced CDH

The excitability of the dorsal horn as well as trigeminal caudalis neurons is under the strong influence of supraspinal controls. A number of brain stem nuclei exert their nociceptive modulation effect via the downward projection to the spinal dorsal horn. The belief has long been held that 5-HT plays a pivotal role in the process of endogenous pain modulation. Several lines of evidence have shown that the analgesic efficacy of various pain control measures is possibly mediated via this neurotransmitter. For instance, Linderoth *et al.* [26] demonstrated that electrical stimulation of the dorsal column, a measure that is used for pain attenuation, can increase in tissue levels of 5-HT in the spinal dorsal horn. Recent evidence has indicated that antinociceptive efficacy of various analgesics, either narcotic or non-narcotic, depends on the integrity of the central 5-HT system. An increase in tissue levels of 5-HT has been observed after administration of analgesic compounds. Pini *et al.* [27] showed that an acute administration of acetaminophen could increase the levels of 5-HT in the cerebral cortex and pons. An increased tissue level of 5-HT was also observed in the spinal cord after a systemic administration of a nonsteroidal anti-inflammatory drug, diclofenac [28]. Therefore, alteration of this system can change the pain susceptibility, thus resulting in the development of chronic pain syndromes. Failure of the serotonergic analgesia has also been proposed to underlie the pathogenesis of fibromyalgia, the syndrome characterized by widespread aching and pain [29].

The abuse of analgesics is an important factor that accounts for the development of CDH. Accumulating evidence showed that analgesics may be involved in this process by interfering with the 5-HT-dependent endogenous analgesia system. Alterations in this neurotransmitter system have been demonstrated in the patients with medication-induced CDH. Platelet 5-HT content has been observed to be decreased in these patients [30,31,32•]. This change is reversible because it can be normalized after drug withdrawal [33]. A decrease in 5-HT content coincided with an upregulation in 5-$HT_{2A}$ receptors on platelet membrane that was also reversible after drug discontinuation [34,35]. This finding is in accordance with the observation that chronic analgesic consumption has a significant effect on signal transduction mechanism. In 1993, Hering *et al.* [36] found that analgesic withdrawal can induce a normalization of the abnormally upregulated thrombin-stimulated inositol phosphate production in platelet in a time-dependent manner. They also found that this downregulation correlated with the improvement of headache. The reduction of platelet 5-HT content is possibly secondary to the abnormal release mechanism, as evident by an observation of abnormal dilatation of intraplatelet canaliculi [31]. More recently, Sarchielli *et al.* [32•] showed that platelet, taken from the analgesic abuse migraineurs, exerts an increase in nitric oxide and cyclic GMP production as well as increases intracytosolic calcium after stimulation with collagen. This evidence implies the alteration of platelet 5-HT system in this condition.

The hypothesis of analgesic-induced derangement in the 5-HT system has been furtherly determined in the central nervous system. Srikiatkhachorn *et al.* [37,38•] demonstrated that the density of the 5-$HT_{2A}$ serotonin receptors rapidly changes in response to analgesic administration. A 15-day course of acetaminophen led to a downregulation of the 5-$HT_{2A}$ receptor and an upregulation of the 5-HT transporter in the frontal cortex. These changes were accompanied by an increase in 5-HT levels in platelets. Because changes in the platelet and the neuronal 5-HT system were demonstrated to be parallel, the observed change in the platelet 5-HT reported here may reflect the concurrent change in the 5-HT level in the central nervous system [39]. A higher degree of the 5-HT receptor and transporter plasticity was observed in animals receiving the higher dose of acetaminophen. Interestingly, the degree of receptor downregulation as well as transporter upregulation became less evident after a more prolonged administration of the drug. The decreases in degree of receptor downregulation and transporter upregulation coincide with the decrease in analgesic efficacy of acetaminophen. The same correlation between the pattern of receptor plasticity and antinociceptive efficacy has been observed by Pini *et al.* [40] in their study on the effect of acetylsalicylate. These findings suggest that chronic analgesic consumption can alter the central 5-HT system.

The findings in the human platelet model and in animals suggest that chronic analgesic exposure can alter the 5-HT system by induction of the low 5-HT state. It has recently been shown that the cerebral microvascular dilatation in response to systemic administration of nitroglycerin, a nitric oxide-donating compound, was enhanced in the 5-HT-depleted animals [41]. This observation might be interesting because nitric oxide is believed to be involved in the pathogenesis of migraine headache. The depletion of 5-HT will subsequently lead to the upregulation of the 5-$HT_2$ receptor as well as the change in the intracellular signaling mechanism. This alteration in the central pain modulation system may account for the perpetuation of headache via several possible mechanisms. The reduction of the nociceptive inhibitory control may enhance the process of central sensitization, activate the nociceptive facilitating system, or enhance the process of kindling. It has been observed that the 5-$HT_{2A}$ receptor may have a nociceptive-potentiating effect by enhancing the release of substance P from the primary afferent [42]. Supraspinal mechanism of this 5-$HT_{2A}$-induced nociceptive facilitation has also been suggested [43]. Because hydrolysis of phosphoinositol is a transduction cascade of this receptor type, the occupation of these receptors will activate the release of calcium from its intracellular store and increase the cytoplasmic calcium concentration. A rising in the intracellular calcium is an important step in the development of long-term potentiation and central sensitization. Therefore, an upregulation of this type of receptor as a result of chronic medication use may increase the sensitivity to pain perception and result in the CDH.

## Conclusions and Hypothesis

Based on available evidence, it can be proposed that central sensitization is a possible mechanism of the development of CDH. Repeated activation of trigeminal nociceptors can lead to the wind-up, and finally sensitization of higher-order nociceptive-processing neurons in the central nervous system. This phenomenon resembles the process of kindling, which underlies the development of epileptogenic focus. Derangement in the endogenous 5-HT-dependent antinociceptive system, either by chronic analgesic consumption or associated psychiatric conditions, might facilitate this process (Fig. 3). The reduction of this transmitter can lead to an upregulation of its postsynaptic 5-$HT_{2A}$ receptor. Activation of these receptors will increase the intracellular calcium via the process of phosphoinositol hydrolysis. The rise in the intracellular calcium then facilitates the process of central sensitization as well as other long-term plasticity in the neurons of the nociceptive pathway. Because activation of the NMDA receptor and the rising of intracellular calcium are important steps in the biochemical process of sensitization, modulation of both steps may be possible treatment targets [44,45].

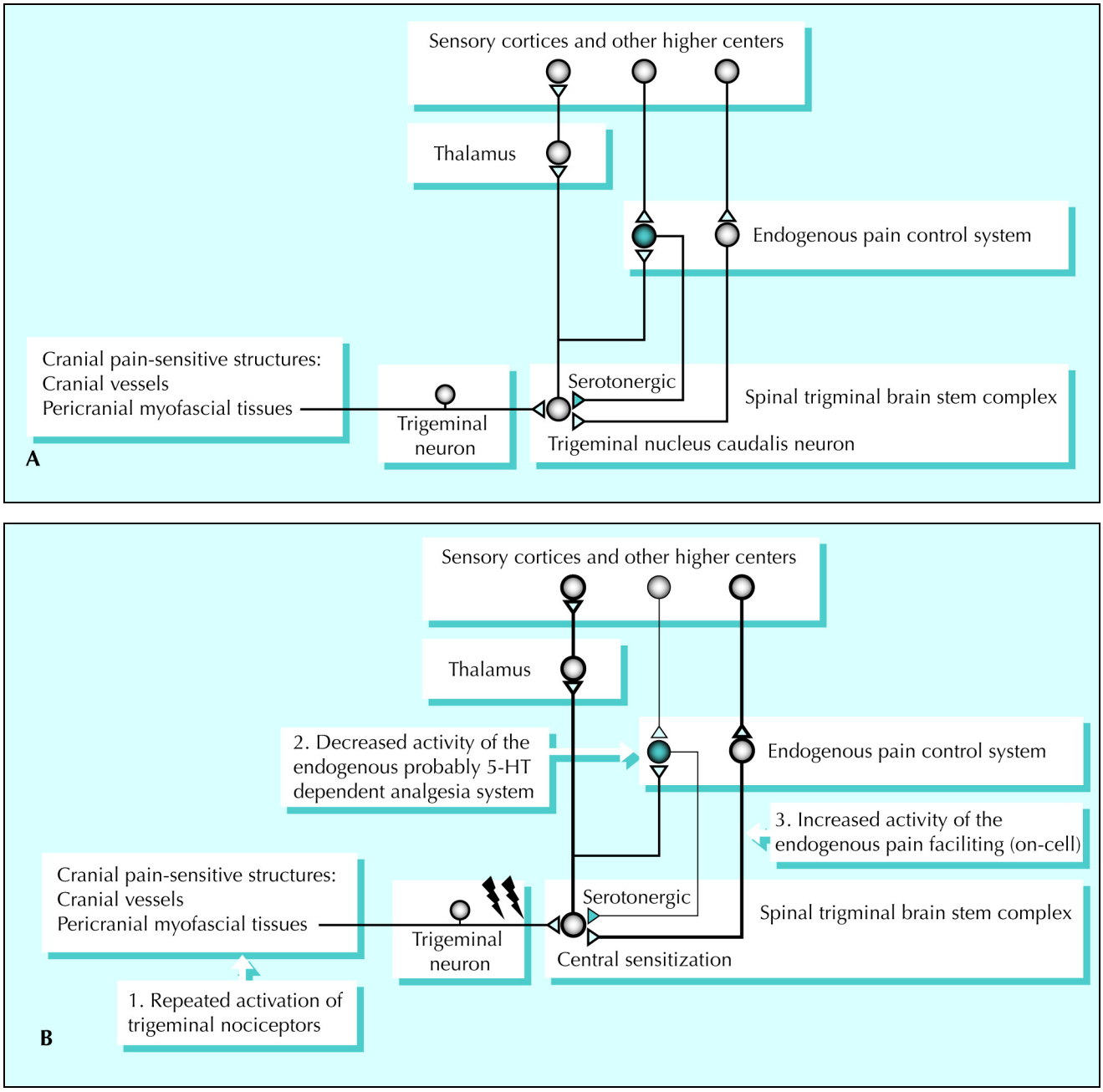


**Figure 3.** Possible mechanisms involved in the development of chronic daily headache. **A,** The activity of the thalamic projection neurons in the trigeminal nucleus caudalis is controlled by both peripheral input and segmental and supra-segmental influence. The repetitive activation of trigeminal nociceptors will trigger the processes of wind-up and central sensitization. **B,** Any factors leading to the derangement in the endogenous pain control system either by attenuating the analgesia system or by enhancing the pain-facilitating systems will expedite this process.

## References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance


1. Silberstein SD, Lipton R, Solomon S, Mathew N: **Classification of daily and near daily headaches: proposed revisions to the IHS classification.** *Headache* 1994, **34:**1–7.
2. Srikiatkhachorn A, Phanthumchinda K: **Prevalence and clinical features of chronic daily headache in a headache clinic.** *Headache* 1997, **37:**277–280.
3. Wang SJ, Fuh JL, Lu SR, *et al.*: **Chronic daily headache in Chinese elderly: prevalence, risk factors, and biannual follow-up.** *Neurology* 2000, **54:**314–319.
4. Spierings Ranke AH, Schroevers M, Honkoop PC: **Chornic daily headache: a time perspective.** *Headache* 2000, **40:**306–310.
5. Sakai F, Ebihara S, Akiyama M, Horikawa M: **Pericranial muscle hardness in tension-type headache. A non-invasive measurement method and its clinical application.** *Brain* 1995, **118:**523–531.
6. Ashina M, Bendtsen L, Jensen R, *et al.*: **Muscle hardness in patients with chronic tension-type headache: relation to actual headache state.** *Pain* 1999, **79:**201–205.
7. Silberstein SD, Mathew N, Saper J, Jenkins S: **Botulinum toxin type A as a migraine preventive treatment.** *Headache* 2000, **40:**445–450.
8. Klapper JA, Klapper A: **Use of botulinum toxin in chronic daily headaches associated with migraine.** *Headache Q* 1999, **10:**141–143.
9. Smuts JA, Baker MK, Smuts HM, *et al.*: **Prophylactic treatment of chronic tension-type headache using botulinum toxin type A.** *Eur J Neurol* 1999, **6:**S99–S102.
10. Evers S, Voss H, Bauer B, *et al.*: **Peripheral autonomic potentials in primary headache and drug-induced headache.** *Cephalalgia* 1998, **18:**216–221.
11. • Ji RR, Woolf CJ: **Neuronal plasticity and signal transduction in nociceptive neurons: implications for the initiation and maintenance of pathological pain.** *Neurobiol Dis* 2001, **8:**1–10.

Summarized the plasticity of the nociceptive system and changes in the signal transduction cascades involved in the pathophysiologic process underlying the development of pathologic pain. Details of the biochemical mechanism were described.

12. Burstein R, Yamamura H, Malick A, Strassman AM: **Chemical stimulation of the intracranial dura induces enhanced responses to facial stimulation in brain stem trigeminal neurones.** *J Neurophysiol* 1998, **79:**964–982.
13. •• Burstein R, Cutrer MF, Yarnitsky D: **The development of cutaneous allodynia during a migraine attack clinical evidence for sequential recruitment of spinal and supraspinal nociceptive neurones in migraine.** *Brain* 2000, **123:**1703–1709.

Described the temporal pattern of cutaneous allodynia developed during the migrainous attack. Based on this finding, the authors suggest that higher-order neurons are sequential sensitized, and thus emphasize the role of central sensitization in the development of headache and cutaneous allodynia.

14. Burstein R, Yarnitsky D, Goor-Aryeh I, *et al.*: **An association between migraine and cutaneous allodynia.** *Ann Neurol* 2000, **47:**614–624.
15. Malick A, Burstein R: **Peripheral and central sensitization during migraine.** *Funct Neurol* 2000, **15(suppl 3):**28–35.
16. •• Bendtsen L: **Central sensitization in tension-type headache—possible pathophysiological mechanisms.** *Cephalalgia* 2000, **20:**486–508.

Extensively reviewed the evidence in support of the role of central sensitization in the development of chronic tension-type headache. The possible hypothesis was proposed.

17. Staud R, Vierck CJ, Cannon RL, *et al.*: **Abnormal sensitization and temporal summation of second pain (wind-up) in patients with fibromyalgia syndrome.** *Pain* 2001, **91:**165–175.
18. Kleinbohl D, Holzl R, Moltner A, *et al.*: **Psychophysical measures of sensitization to tonic heat discriminate chronic pain patients.** *Pain* 1999, **81:**35–43.
19. Fusco BM, Colantoni O, Giacovazzo M: **Alteration of central excitation circuits in chronic headache and analgesic misuse.** *Headache* 1997, **37:**486–491.
20. Schnider P, Maly J, Grunberger J, *et al.*: **Improvement of decreased critical flicker frequency (CFF) in headache patients with drug abuse after successful withdrawal.** *Headache* 1995, **35:**269–272.
21. Schnider P, Maly J, Mraz M, *et al.*: **MMPI and critical flicker frequency (CFF) analysis in headache patients with and without drug abuse.** *Headache* 1995, **35:**17–20.
22. Evers S, Schmidt F, Bauer B, *et al.*: **The impact of ergotamine-induced headache and ergotamine withdrawal on information processing.** *Psychopharmacology* 1999, **142:**61–67.
23. Roon KI, Bakker D, van Poelgeest MI, *et al.*: **The influence of ergotamine abuse on psychological and cognitive functioning.** *Cephalalgia* 2000, **20:**462–469.
24. Schoenen J, Maertens de Noordhout A, Timsit-Berthier M, Timsit M: **Contingent negative variation (CNV) as a diagnostic and physiologic tool in headache patients.** In *Migraine: Clinical and Research Advances.* Edited by Clifford RF. Basel: Kager; 1985:17–25.
25. Siniatchkin M, Gerber WD, Kropp P, Vein A: **Contingent negative variation in patients with chronic daily headache.** *Cephalalgia* 1998, **18:**565–569.
26. Linderoth B, Gazelius B, Franck J, Brodin E: **Dorsal column stimulation induces release of serotonin and substance P in the cat dorsal horn.** *Neurosurgery* 1992, **31:**289–297.
27. Pini LA, Sandrini M, Vitale G: **The antinociceptive action of paracetamol is associated with changes in the serotonergic system in the rat brain.** *Eur J Pharmacol* 1996, **308:**31–40.
28. Björkman R: **Central antinociceptive effects of non-steroidal anti-inflammatory drugs and paracetamol. Experimental studies in the rat.** *Acta Anaesthesiol Scand* 1995, **39(suppl 103):**1–44.
29. Nicolodi M, Volpe AR, Sicuteri F: **Fibromyalgia and headache. Failure of serotonergic analgesia and N-methyl-D-aspartate-mediated neuronal plasticity: their common clues.** *Cephalalgia* 1998, **18(suppl 21):**41–44.
30. Srikiatkhachorn A, Anthony M: **Platelet serotonin in patients with analgesic induced headache.** *Cephalalgia* 1996, **16:**423–426.
31. Srikiatkhachorn A, Maneesri S, Govitrapong P, Kasantikul V: **Derangement of serotonin system in migraine patients with analgesics abuse headache: clues from platelets.** *Headache* 1998, **38:**43–49.
32. • Sarchielli P, Alberti A, Russo S, *et al.*: **Nitric oxide pathway, Ca2+, and serotonin content in platelets from patients suffering from chronic daily headache.** *Cephalalgia* 1999, **19:**810–816.

Using the platelet as a neuronal model, the authors demonstrated the occurrence of an activation of cGMP-Ca2+ mediated events in CDH patients with analgesic abuse. They also suggested that the physiologic compensatory mechanism, which intervenes in overcoming the increase in cytosolic Ca2+ levels, is not efficient in these patients due to the depletion of serotonin.

33. Hering R, Glover V, Pattichis K, *et al.*: **5HT in migraine patients with medication-induced headache.** *Cephalalgia* 1993, **13:**410–412.
34. Srikiatkhachorn A, Anthony M: **Serotonin receptor adaptation in patients with analgesic induced headache.** *Cephalalgia* 1996, **16:**419–422.
35. Srikiatkhachorn A, Puangniyom S, Govitrapong P: **Plasticity of 5-HT2A serotonin receptor in patients with analgesic-induced transformed migraine.** *Headache* 1998, **38:**534–539.
36. Hering R, Gardiner I, Catarci T, *et al.*: **Cellular adaptation in migraineurs with chronic daily headache.** *Cephalalgia* 1993, **13:**261–266.
37. Srikiatkhachorn A, Tarasub N, Govitrapong P: **Acetaminophen-induced antinociception via central 5-HT2A receptors.** *Neurochem Int* 1999, **34:**491–498.

38.• Srikiatkhachorn A, Tarasub N, Govitrapong P: **Effect of chronic analgesic exposure on the central serotonin system. A possible mechanism of analgesic abuse headache.** *Headache* 2000, **40:**343–350.
Described the plasticity of the central serotonergic system after chronic paracetamol administration. The authors showed that the degree of 5-$HT_{2A}$ receptor downregulation and 5-HT transporter upregulation became minimized after chronic analgesic exposure. The relationship between these biochemical changes and the development of CDH was discussed.
39. Ostrowski S, Rao ML, Redei J, Andres AH: **Concurrence of cortex and platelet serotonin 2 receptor binding characteristics in the individual and the putative regulation by serotonin.** *J Neural Transm Gen Sect* 1993, **93:**27–35.
40. Pini LA, Vitale G, Sandrini M: **Serotonin and opiate involvement in the antinociceptive effect of acetylsalicylic acid.** *Pharmacology* 1997, **54:**84–91.
41. Srikiatkhachorn A, Anuntasethakul T, Maneesri S, *et al.*: **Hyposerotonin-induced nitric oxide supersensitivity in the cerebral microcirculation.** *Headache* 2000, **40:**267–275.
42. Eide PK, Hole K: **Interactions between serotonin and substance P in the spinal regulation of nociception.** *Brain Res* 1991, **550:**225–230.
43. Alhaider AA: **Antinociceptive effects of ketanserin in mice: involvement of supraspinal 5-HT2 receptors in nociceptive transmission.** *Brain Res* 1991, **543:**335–340.
44. Eide PK: **Wind-up and the NMDA receptor complex from a clinical perspective.** *Eur J Pain* 2000, **4:**5–15.
45. Nicolodi M, Del Bianco PL, Sicuteri F: **Modulation of excitatory amino acids pathway: a possible therapeutic approach to chronic daily headache associated with analgesic drugs abuse.** *Int J Clin Pharmacol Res* 1997, **17:**97–100.