Neurotoxins in the Neurobiology of Pain

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Migraine is a common, chronic, incapacitating, neurovascular disorder that affects an estimated 12% of the population. Understanding the basic mechanisms of pain is important when treating patients with chronic pain disorders.

Pain, an unpleasant sensory and emotional experience, is usually triggered by stimulation of peripheral nerves and often associated with actual or potential tissue damage. Peripheral nerve fibers transmit pain signals from the periphery toward the spinal cord or brain stem. The different diameter pain fibers (A and C) vary in the speed of conduction and the type of pain transmitted (eg, sharp versus dull). When stimulated, peripheral pain fibers carrying sensory input from the body enter at different layers of the dorsal horn, which is then propagated toward the thalamus via the spinothalamic tract within the spinal cord. Conversely, sensory input from the face does not enter the spinal cord but enters the brain stem via the trigeminal nerve.

This review describes in detail the neurobiological mechanisms and pathways for pain sensation, with a focus on migraine pain.

Key words: migraine, pain, mechanism, trigeminal nucleus

Abbreviations: STT spinothalamic tract, VPL ventroposterior lateral

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Migraine is a common, chronic, incapacitating, neurovascular disorder that affects an estimated 12% of the population.¹ Migraine attacks are characterized by episodes of throbbing head pain that may be severe. Understanding the basic mechanisms of pain is important when treating patients with chronic pain disorders.

Pain is an unpleasant sensory and emotional experience usually triggered by stimulation of peripheral nerves and often associated with actual or potential tissue damage. The intracranial pain-sensitive structures include the glossopharyngeal, vagus, trigeminal, and upper cervical spinal nerves; the vascular structures of the venous sinuses and their tributaries; the dural arteries; the carotid, vertebral, and basilar arteries; the circle of Willis; and the proximal portions of the cerebral, vertebral, and basilar branches.² Surrounding the large cerebral vessels, pial vessels, large venous sinuses, and dura mater is a plexus of largely unmyelinated fibers that arise from the ophthalmic division of the trigeminal ganglion and, in the posterior fossa, the upper cervical dorsal roots. This review describes the neurobiological mechanisms and pathways for pain sensation.

PAIN SENSORY FIBERS

Peripheral nerves vary in diameter, with fiber size correlating with function. Large fibers conduct faster than small fibers; myelinated fibers conduct faster than unmyelinated fibers. The compound action potential of a peripheral nerve has 3 distinct deflections: A being the fastest; B, the intermediate; and C, the slowest. The A fibers, which are responsible for the A deflection, are myelinated sensory and motor fibers. The A deflection is subdivided further into alpha, beta, gamma, and delta peaks, with A alpha fibers the largest and most rapidly conducting myelinated fibers, and A delta fibers the smallest and...
slowest of the A group of fibers. The B fibers are myelinated visceral fibers (preganglionic autonomic fibers and some visceral afferents). The C fibers are small-caliber, unmyelinated, and slow-conducting fibers.

For the most part, nociceptors are free nerve endings found throughout almost all human tissue. There are 4 classes of nociceptors: thermal, mechanical, polymodal, and silent nociceptors. Some free nerve endings (silent nociceptors) respond poorly to all stimuli. Their firing threshold is dramatically reduced by inflammation and various chemical insults that may contribute to the development of secondary hyperalgesia and central sensitization. Activation of silent nociceptors is thought to contribute to pain that accompanies inflammation and certain pathological processes.

Pain evoked by different input channels represents activation of high-threshold receptor ion-channel transducers in nociceptor peripheral terminals (nociceptive transduction). The mechanism by which noxious stimuli depolarize free sensory endings and generate action potentials is not known. The membrane of the nociceptor, however, is thought to contain proteins that convert the thermal, mechanical, or chemical energy of noxious stimuli into a depolarizing electrical potential. One such protein is the receptor for capsaicin, a natural product of hot peppers. The capsaicin, or vanilloid, receptor is found exclusively in primary afferent nociceptors and mediates the pain-producing actions of capsaicin. The capsaicin receptor responds to noxious heat stimuli, which suggests that it is a transducer of painful heat stimuli. Local inhibition occurs at different relay levels in the neuraxis. Descending inhibition originates in the forebrain and brain stem and terminates in the brain stem and spinal cord. Factors responsible for the local inhibition include decreased activation of neurons, down-regulation of receptors and transmitters, and cell death (disinhibition).

Nociceptors are associated with either unmyelinated C fibers; small, thinly myelinated A delta fibers; or, under certain circumstances, A beta fibers. Thermal and mechanical nociceptors are associated with small-diameter, thinly myelinated A delta fibers that conduct signals at about 5 to 30 m/s. Polymodal nociceptors, activated by high-intensity mechanical, chemical, or thermal (both hot and cold) stimuli, are associated with small-diameter, nonmyelinated C fibers that conduct slowly, generally at velocities of less than 1 m/s, and are responsible for dull pain and temperature sensitivity. Neurotransmitters within these fibers include glutamate and the neuropeptides, substance P, calcitonin gene-related peptide (CGRP), and neurokinin A. Stimulation of C fibers results in the slow buildup of an aching, throbbing, or burning pain, whereas faster-conducting A delta fibers transmit sharper initial pain sensations. For example, if you were to stick yourself with a pin, the initial sharp pain would be due to activation of the A delta fibers. After a lag of about 1 second, the sharp pain would be followed by a dull pain. The time delay in the 2 types of pain sensation is explained by the fact that A delta fibers transmit much faster than C fibers.

In contrast, A beta fibers normally do not transmit pain. The neurotransmitters within these nerve fibers consist mainly of excitatory amino acids, such as glutamate and aspartate. Even so, following activation or injury, the expression of several neuropeptides such as neuropeptide Y, galanine, cholecystokinin, and substance P, is augmented. As a result, sensory information that is normally transduced from touch and vibration may be perceived as painful. In the absence of conduction of A alpha and A beta fibers, the perception of pain is not normal (eg, when pinprick, pinch, or ice cannot be distinguished from each other and instead each produces the sensation of burning pain).

Action potentials initiated by a painful stimulus travel both centrally, toward the spinal cord or brain stem, and peripherally, invading branches of the same neuron outside the area of injury (axon reflex). Peripherally released neuropeptides cause dilation of arterioles (flare), leakage of plasma from venules (edema), and inflammation. In the meninges, they produce neurogenic inflammation with plasma protein extravasation. Nociceptors contain glutamate receptors, and glutamate is thought to play a role in peripheral sensitization.

**PAIN PATHWAYS**

The principal ascending spinal pain pathway is the lateral spinothalamic tract (STT). Originating from both lamina I and deep layers V-V1 of the doro-
sal horn, the STT receives synaptic input from primary nociceptive afferent neurons. The main projection of this pathway is to the ventroposterior lateral (VPL) nucleus of the thalamus and, from there, to the primary and secondary somatosensory cerebral cortical areas (S1 and S2) (the STT-VPL-S1-S2 pathway). The STT-VPL-S1-S2 pathway’s neurons of origin within the dorsal horn contain predominantly wide dynamic-range neurons and some nociceptive-specific neurons that are critical for both sensory and affective pain processing.

The fifth cranial nerve, arising from the trigeminal ganglion (semilunar or gasserian ganglion), has 3 divisions: ophthalmic, mandibular, and maxillary. Anterior pain-producing structures are innervated by the ophthalmic (first) division. Posterior regions are subserved by upper cervical nerves. Central trigeminal primary afferent processes form the sensory root of the trigeminal nerve, enter the brain stem at the pontine level, and terminate in the trigeminal brain stem nuclear complex. The trigeminal brain stem nuclear complex is composed of the principal trigeminal nuclei and spinal trigeminal nuclei (subdivided into the rostral subnuclear oralis, middle subnuclear interpolaris, and caudal subnuclear caudalis). All contribute to facial and cranial nociception.

The brain stem spinal trigeminal nucleus is analogous to the dorsal horn of the spinal canal, the first synapse in the central nervous system. Most spinothalamic and trigeminothalamic tract neurons that originate from the dorsal horn and project to VPL and VPM nuclei have wide dynamic-range characteristics. Second-order neurons from the trigeminal spinal nuclei form the trigeminothalamic tract and project to other midbrain structures, as well as to the thalamic tract. A number of secondary neuronal

Fig 1.—Development of cutaneous allodynia during a migraine attack.
pathways for pain also project to the somatosensory cortex, insular cortex, and cingulate cortex.

A reflex connection exists between neurons in the pons in the superior salivatory nucleus, which results in a cranial parasympathetic outflow that is mediated through the pterygopalatine, otic, and carotid ganglia. This normal trigeminal-autonomic reflex may be hyperactive in patients with trigeminal-autonomic cephalgias (cluster headache and paroxysmal hemi-crania) and perhaps migraine.

Most trigeminal brain stem nuclear complex neurons that project to the contralateral thalamus are found in the principal trigeminal nuclei. The remaining neurons are located in the middle subnuclear interpolaris, with smaller contributions from the rostral subnuclear oralis and caudal subnuclear caudalis. The contralateral fibers from the principal trigeminal nuclei ascend with the medial lemniscus and are often referred to as the trigeminal lemniscus. The trigeminotectal projections terminate preferentially in the thalamic VPM nucleus.

Most VPM nuclei, some with wide dynamic-range characteristics, respond to low-threshold stimuli. The trigeminal brain stem nuclear complex neurons also project to a number of diencephalic and brain stem areas involved in the regulation of autonomic, endocrine, affective, and motor functions. All trigeminal brain stem nuclear complex neuron subnuclei project directly to the hypothalamus.

Unlike the STT-VPL-S\textsubscript{1-2} pathway, other ascending pathways have a preponderance of nociceptive-specific neurons. The spino-parabrachio-amygdaloid pathway and the spino-parabrachio-hypothalamic pathway consist exclusively of nociceptive-specific neurons. These pathways are involved in autonomic processes and behaviors related to fear and defense. Spinothalamic and trigeminotectal tract neurons that terminate in the ventromedial portion of the posterior nuclear complex and ventrocaudal portion of the mediodorsal nucleus have more nociceptive-specific neurons.

Thus, there are functionally different ascending pain pathways: (1) the STT-VPL-S\textsubscript{1-2} pathway, which contains mostly wide dynamic-range neurons important for encoding the capacity to recognize the sensory intensity and sensory qualitative features of pain; and (2) other pathways, which contain mostly nociceptive-specific neurons that are important for immediate affective-motivational responses, autonomic and somatomotor activation, and possibly pain sensation.

Pain has both sensory and affective dimensions. In addition to being physically unpleasant, pain is associated with negative emotions shaped by context, anticipations, and attitudes. The somatosensory cortex is involved in pain affect. Pain unpleasantness is in series with pain sensation intensity. Pain sensations and affect are disrupted by STT-VPL-S\textsubscript{1-2} lesions because this pathway makes serial interconnections to corticollimbic structures involved in pain-related affect.

The anterior cingulate cortex is part of the brain’s attentional and motivational network, projecting to prefrontal (executive functions) and supplementary motor cortex (response selection) regions. It coordinates inputs from parietal areas involved in the perception of bodily threat with frontal cortical areas involved in the plans and response priorities for pain-related behavior. The anterior cingulate cortex is the most consistent brain region activated in brain imaging studies of pain.

Input to lower brain stem and limbic structures may contribute to arousal, autonomic, and somatomotor activation. Medial thalamic nuclei project to regions involved in monitoring the overall state of the body (insula cortex), directing attention (anterior cingulate cortex), and assigning response priorities (anterior cingulate cortex). In addition, the anterior cingulate cortex receives input from a ventrally directed somatosensory-limbic pathway that contributes varying degrees of cognitive evaluation to pain affect.

**POTENTIAL MECHANISMS OF PAIN**

Pain can be assessed at different levels—the individual level (personal suffering), the system level (how pain is generated), and the cellular and molecular level (change in the individual elements of the system)—and is mediated by different input channels. Usually, the pain from intensive stimulation or injury (nociceptive pain) diminishes as healing progresses.
Even so, another type of pain can occur with peripheral or central nervous system malfunction. Three spatiotemporal characteristics of pain can be seen during both normal and pathophysiological pain: (1) as pain intensity increases, the area in which it is experienced often enlarges (radiation); (2) the pain may outlast the evoking stimulus; and (3) repeated nociceptive stimuli may increase the perceived pain intensity, even without increased input (sensitization). Pain was initially believed to be a fixed line system activated in the periphery by nociceptors in response to an adequate noxious stimulus. Although true of nociceptive pain, it is not the case for pain hypersensitivity or spontaneous pain, where a number of different input channels can lead to the sensation of pain. These input channels include: (1) nociceptor activation in the periphery by noxious mechanical, thermal, or chemical stimuli (nociceptive pain); (2) activation of sensitized nociceptors in the periphery by low-intensity stimuli (peripheral sensitization); (3) ectopic discharge in nociceptors, originating at a neuroma, dorsal root ganglion, peripheral nerve, or dorsal root (Peripheral nerve injury); (4) low-threshold afferent activation in the periphery by low-intensity mechanical or thermal stimuli in combination with central sensitization, synaptic reorganization, or disinhibition; (5) ectopic discharge in low-threshold afferents originating at a neuroma, dorsal root ganglion, peripheral nerve, or dorsal root (Peripheral nerve injury associated with central sensitization, synaptic reorganization, or disinhibition); and (6) spontaneous activity in central neurons (in the dorsal horn, thalamus, or cortex).

Pain results from: (1) nociceptive transduction; (2) peripheral sensitization; (3) changes in ion-channel expression/phosphorylation/accumulation in primary afferents (altered sensory neuron excitability); (4) posttranslational changes in ligand- and voltage-gated ion-channel kinetics in central (spinal cord and brain) neurons, altering their excitability and the strength of their synaptic inputs (central sensitization); (5) alterations in the expression of receptors/transmitters/ion channels in peripheral and central neurons (phenotype modulation); (6) modification of synaptic connections caused by cell death or sprouting (synaptic reorganization); and (7) loss of local inhibition at different relay levels in the neuraxis and descending inhibition caused by decreased activation of neurons, down-regulation of receptors/transmitters, and cell death, originating in the forebrain and brain stem and terminating in the brain stem and spinal cord (disinhibition).

The mammalian nervous system contains networks that modulate nociceptive transmission. The trigeminal brain stem nuclear complex receives monoaminergic, enkephalinergic, and peptidergic projections from regions known to be important in the modulation of nociceptive systems. A descending inhibitory neuronal network extends from the frontal cortex and hypothalamus through the periaqueductal gray to the rostral ventromedial medulla and the medullary and spinal dorsal horn. The rostral ventromedial medulla includes the nucleus raphe magnum and the adjacent reticular formation and projects to the outer laminae of the spinal and medullary dorsal horn. Electrical stimulation or injection of opioids into the periaqueductal gray or rostral ventromedial medulla reduces nocireponsive neuron activity. The periaqueductal gray receives projections from the insular cortex and the amygdala.

Antinociception can be measured by nociceptive reflex inhibition. In the rostral ventromedial medulla and periaqueductal gray, 3 classes of neurons have been identified. “Off-cells” pause immediately before the nociceptive reflex, whereas “on-cells” are activated. Neutral cells show no consistent changes in activation. Opioids activate off-cells and inhibit on-cells; nociceptive reflexes are inhibited. Thus, off-cell activity is related to suppression of nociception, whereas on-cell activity is accompanied by enhancement to noxious stimuli. On- and off-cell activity is modulated by 5-HT1 receptor agonists.

These cells are believed to modulate the activity of the trigeminal nucleus caudalis and dorsal horn neurons. Increased on-cell activity in the brain stem’s pain modulation system could enhance the response to both painful and nonpainful stimuli. Opiate withdrawal results in increased firing of on-cells, decreased firing of off-cells, and enhanced nociception. Headache may be caused, in part, by enhanced neuronal activity in the nucleus caudalis as a result of enhanced on-cell or decreased off-cell ac-
tivity. Other conditioned stimuli associated with pain and stress also can turn on the pain system and may account, in part, for the association between pain and stress.

Although much is known about the mechanisms that operate in primary afferent and dorsal horn neurons to produce pain, much less is known about the changes that occur in the brain and how the affective, cognitive, and perceptual aspects of pain are generated. It is clear, however, that the sensory cortex can undergo considerable plasticity in concert with the changes that occur in subcortical structures, and such supraspinal plasticity is likely to play a major role in shaping the global pain experience.

Pain perception can be modulated by psychological factors, such as attention, stress, and arousal. Placebo and nocebo manipulations (giving inert agents with suggestions for reducing or enhancing symptoms), hypnotic suggestion, attention, distraction, and emotions modulate pain-inhibitory and pain-facilitation pathways. Our understanding of how this modulation occurs at a neuroanatomical level has been significantly enhanced using functional neuroimaging. Brain imaging experiments show that anticipation of pain affects cortical nociceptive regions. Interestingly, these brain regions are the same ones that are directly activated during pain itself. Tracey et al neuroanatomically defined a key area in the network of brain regions active in response to pain that is modulated by attention to the painful stimulus.

High-resolution functional magnetic resonance imaging was used in 9 control subjects to define brain activation within the periaqueductal gray region in response to painful heat stimulation applied to the hand. Subjects were asked to either focus on or distract themselves from painful stimuli, which were cued using colored lights. During the distraction condition, subjects rated pain intensity significantly lower than when they attended to the stimulus. Activation in the periaqueductal gray region was significantly increased during the distraction condition, and the total increase in activation was predictive of changes in perceived intensity. These results provide direct evidence supporting the notion that the periaqueductal gray region is a site for higher cortical control of pain modulation in humans, which is entirely consistent with the known concept that the more attention is focused on pain, the worse it gets.

**PAIN IN MIGRAINE**

Migraine is a primary brain disorder, a form of neurovascular headache in which neural events result in dilation of blood vessels, with further pain and nerve activation. Migraine most likely results from dysfunction of brain stem pathways that normally modulate sensory input. Three components seem to be involved: (1) the cranial blood vessels, (2) the trigeminal innervation of the vessels, and (3) the reflex connections of the trigeminal system with the cranial parasympathetic outflow. The key pathway for the pain is trigeminovascular input from the meningeal vessels. Brain imaging studies suggest that important modulation of the trigeminovascular nociceptive input stems from the dorsal raphe nucleus, locus coeruleus, and nucleus raphe magnus.

During a migraine attack, there is an inflammatory process (neurogenic inflammation) that occurs at the site of the nerve terminal. Trigeminal nerve activation is accompanied by the release of vasoactive neuropeptides including CGRP, substance P, and neurokinin A from the nerve terminals. These mediators produce mast cell activation, sensitization of the nerve terminals, and extravasation of fluid into the perivascular space around the dural blood vessels. Intense neuronal stimulation causes induction of c-fos (an immediate early gene product) in the trigeminal nucleus caudalis of the brain stem. Substance P and CGRP further amplify the trigeminal terminal sensitivity by stimulating the release of bradykinin and other inflammatory mediators from nonneuronal cells. Cortical spreading depression (the cause of the aura) can activate the trigeminal system. Although the brain itself is largely insensate, pain can be generated by large cranial vessels, proximal intracranial vessels, or dura mater. The involvement of the ophthalmic division of the trigeminal nerve and its overlap of structures innervated by branches of C2 nerve roots explain the typical distribution of migraine pain over the frontal and temporal regions and the referral of pain to the parietal, occipital, and high cervical regions.
CENTRAL SENSITIZATION IN PAIN AND MIGRAINE

Sensitization of nociceptors results in increased spontaneous neuronal discharges. Neurons increase responsiveness to both painful and nonpainful stimuli. Often the receptor fields are expanded and patients feel pain over a greater part of the dermatome. Clinically, this is recognized as hyperalgesia (increased sensitivity to pain) and cutaneous allodynia (pain perceived in response to stimuli that are not necessarily noxious).

Most patients with migraine exhibit cutaneous allodynia inside and outside their pain-referred areas during migraine attacks. Burstein et al studied the development of cutaneous allodynia during migraine by measuring the pain thresholds in the head and forearms of a patient at several points during the migraine attack (1, 2, and 4 hours after onset) and compared the pain thresholds in the absence of an attack. Within 20 to 30 minutes after the initial activation of the patient’s peripheral nociceptors, they became sensitized and mediated the symptoms of cranial hypersensitivity. The barrage of impulses then activated second-order neurons and initiated their sensitization, mediating the development of cutaneous allodynia on the ipsilateral head. The sensitized second-order neurons activated and eventually sensitized third-order neurons, leading to allodynia on the patient’s contralateral head and forearms at the 2-hour measurement, a full hour after the initial allodynia on the ipsilateral head.

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