Understanding Pain

Optimal management of pain and headache disorders is through a multimodal approach that reflects complex pathophysiologic mechanisms.

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Pain is among the most common reasons for seeking medical care and is often the presenting symptom of an underlying disease in either general medicine or neurology. Together, pain and headache disorders impart huge economic and social costs to society. The reported annual prevalence of migraine is 15% globally with significant variation by region; estimated prevalence ranges from 9% in China to 35% in the European Union, whereas prevalence in the US is estimated at 11.7% (17.1% in women vs 5.6% in men). Approximately 2.5% to 3% of those with episodic migraine (<15 headache days/ month or <8 migraine days/ month) will progress to have chronic migraine (≥15 headache days/month or ≥8 migraine days/ month) the following year. Chronic migraine prevalence globally is estimated at 1.4% to 2.2%. Headache disorders are the top reported pain condition costing an estimated 3.5 hours/week in productivity and increased cost of $9,000/year for every individual with migraine.[1]

Considering the prevalence and impact of pain and headache disorders, it should not be surprising that there has been considerable focus on elucidating the different mechanisms of pain and headache, as well as incorporating these into classification and treatment. Although there is still much to understand, current concepts regarding pain pathophysiology—based upon decades of basic, translational, and clinical studies—help explain pain phenomena and conditions seen clinically and can guide treatment of these conditions.

Classifying Pain

The International Association for the Study of Pain (IASP) recently published an updated approach to pain classification that proposes classifying pain into 1 of 3 types based on mechanisms: nociceptive, neuropathic, or nociplastic pain. Nociceptive describes pain caused by the physiologic response to actual or potential tissue damage and is the only type resulting from normal expected sensory function of the nervous system. Neuropathic describes pain caused by direct injury to the peripheral or central somatosensory nervous system (eg, entrapment/compression, diabetic neuropathy, postherpetic neuralgia, chemotherapy-induced neuropathy, and spinal cord injury). Nociplastic, a newly described mechanism, describes pain caused by somatosensory dysfunction in the absence of a nociceptive stimulus or a somatosensory nervous system lesion. Nociplastic pain includes several of the most experienced pain conditions (eg, migraine, fibromyalgia, irritable bowel syndrome [IBS], and pelvic pain syndrome).[2]

Experiencing Pain

Nociceptive Fiber Activation

For pain originating in the periphery (ie, outside the spinal cord or brain), nociception begins with activation of a nociceptor, a specialized nerve ending. Nociceptors may respond to mechanical, thermal, or chemical stimuli when activation thresholds are met. Peripheral nociceptors are associated with Aδ and C fibers. Aδ fibers are thinly myelinated and transmit well-localized pain quickly. Type I Aδ fibers respond more to mechanical and chemical stimuli but have a higher threshold for heat, whereas type II Aδ fibers respond more to heat but have a higher threshold for mechanical stimuli. C fibers are unmyelinated and transmit poorly localized pain more slowly. Most C fibers respond to a variety of different stimuli. Some are called "silent nociceptors" because they respond to heat but not mechanical stimuli unless there is tissue injury or inflammation. Peptidergic C fibers release peptides, mainly substance P and calcitonin gene-related peptide (CGRP).[3]

Signal Transduction

As described, a variety of receptors respond to various noxious stimuli, giving neurons with different receptors different nociceptive properties. Upon activation, these receptors trigger membrane depolarization (ie, a generator potential) that becomes an action potential given adequate magnitude or summation. Well-studied ion channels involved in nociception are the transient receptor potential (TRP) channels TRP vanilloid 1 (TRPV1), TRP ankyrin 1 (TRPA1), and TRP melastatin 8 (TRPM8). TRPV1 responds to heat, acidic environments, capsaicin, and bioactive lipids. Although its temperature sensing threshold is around 43°C, inflammatory molecules and products from second-messenger pathways can sensitize TRPV1 to respond to lower temperatures.[4] Capsaicin modulates TRPV1, contributing to desensitization of nociceptors by multiple mechanisms (eg, depletion of neuropeptides and reversible neuronal degeneration) and has been shown to have modest

effect in treating neuropathic pain.[5] TRPA1 responds to chemical stimuli including nitrogen and oxygen free radicals, and TRPM8 responds to chemicals that cause a cooling sensation (eg, menthol) and to cold (threshold under ~26°C).[4]

Many other ion channels are implicated in nociception. Acid-sensing ion channels (ASICs) react to acidic environments (eg, lactic acid accumulation in the setting of anaerobic metabolism in the heart and musculoskeletal system). TMEM16A is a calcium-activated chloride channel that contributes to membrane depolarization and is activated by bradykinin and heat. Hyperpolarization-activated, cyclic nucleotide-gated cation channels (HCNs) are excitatory channels, some of which are activated by cyclic adenosine monophosphate (cAMP).[4] Voltage-gated sodium channels (Na_v) are also involved in nociception. $Na_v1.7$ has a lower activation threshold and rapid rate of depolarization and repolarization but a slow recovery and amplifies stimuli that would otherwise be below the activation threshold. $Na_v1.8$ has a higher threshold for activation but is the main propagator of C-fiber depolarization. Gain-of-function mutations in $Na_v1.7$ and $Na_v1.8$ are implicated in genetic pain disorders, and loss-of-function mutations in $Na_v1.7$ are implicated in congenital pain insensitivity.[6] Carbamazepine, the only medication approved by the Food and Drug Administration (FDA) for the indication of trigeminal neuralgia, blocks voltage-gated sodium channels to inhibit neurotransmission.[7]

Nociceptors also express a wide variety of potassium channels that inhibit neurons by hyperpolarizing the cell as potassium ions exit. Voltage-gated potassium channels (K_v) modify neuron excitability and activity. Calcium-activated potassium channels (K_{Ca}) are activated by the accumulation of calcium ions at the nerve terminal to provide feedback inhibition. Sodium-activated potassium channels (K_{Na}) hyperpolarize the cell to reduce activity after repetitive firing, and 2-pore potassium channels (K_{2P}) are leak channels that affect resting membrane potential.[6] N-type calcium channels at axon terminals trigger the release of glutamate, substance P, and CGRP. T-type calcium channels control glutamate release in axon terminals in the dorsal horn, and L-type channels are less studied but likely have excitatory effects in these neurons.[6] Gabapentin and pregabalin inhibit voltage-dependent calcium channels and are approved for treating postherpetic neuralgia; pregabalin is also approved for treating diabetic neuropathy.[7]

Axon injury affects ion channel expression at the cell membrane, including increased expression of $Na_v1.7$, $Na_v1.8$, and calcium channels, activation of $Na_v1.7$ via phosphorylation, and decreased expression of $Na_v1.9$ and potassium channels.[6]

Peripheral Sensitization

Peripheral sensitization refers to mechanisms that increase peripheral nociceptor activity such that the nociceptors will respond to previously painless stimuli or even fire spontaneously. In other words, the threshold for activating peripheral nociceptors is lowered by peripheral sensitization.

Chemical mediators released by inflammation or injury contribute to peripheral sensitization. Histamine is released by mast cells after tissue injury. Inflammatory processes release the lipid anandamide, which activates TRPV1. Damaged endothelium and platelets release adenosine triphosphate (ATP), acetylcholine (ACh), and serotonin (5-HT), which, in turn cause release of prostaglandins and bradykinin. Nociceptors are directly stimulated by bradykinin to produce prostaglandins in the arachidonic acid pathway via cyclooxygenase (COX) enzymes that are the target of nonsteroidal anti-inflammatory drugs (NSAIDs). Inflammatory cytokines (eg, interleukin [IL]-1, IL-6, and tumor necrosis factor-α [TNF-α]), induce cells to release nerve growth factor (NGF), which affects expression of ion channels that increase excitability and cause release of brain-derived neurotrophic factor (BDNF) in the dorsal horn.[6,8]

Primary afferent nociceptors release glutamate (the major excitatory neurotransmitter) for fast neurotransmission in the spinal cord. Peptidergic C fibers also release peptides (eg, substance P and CGRP) that are stored in dense core vesicles and require larger calcium ion influx for release compared with smaller glutamate-containing vesicles. Therefore, more persistent stimuli are required for peptide release.[3] When released into the periphery, substance P and CGRP cause vasodilation, increased vascular permeability, and degranulation of other peripheral cells such as mastocytes. As a result, more nociceptive molecules are released to further trigger the nociceptive neurons in the process referred to as neuroinflammation.[9]

Signal Transmission

First-order nociceptive neurons have synapses in the dorsal horn. Aδ fibers synapse in laminas I, V, and outer lamina II. C fibers synapse in laminas I and II. Some neurons in lamina I receive purely nociceptive input, whereas other neurons, referred to as *wide-dynamic-range neurons* receive both nociceptive and nonnociceptive inputs. Lamina I transmits ascending projections, but most neurons in laminas I and II are interneurons, some of which are excitatory and release glutamate, and others of which are inhibitory and release GABA, glycine, or endogenous opioids. Neurons in lamina V also receive input from Aβ fibers that transmit light touch and have dendrites that synapse in outer laminae with axons from C fibers. Neurons in lamina V receive nociceptive, innocuous, somatic, and visceral inputs, which is thought to be the cause of referred pain in which pain from a visceral organ is referred to a somatic area innervated by the same spinal segment.[10,11]

Of the ascending projection neurons, most decussate via the anterior white commissure and project contralaterally, although some project bilaterally.[10] The spinothalamic tract is important for the discrimination of pain location and intensity. Second-order neurons terminate in the ventral posterolateral nucleus (VPL) in the thalamus, then third-order

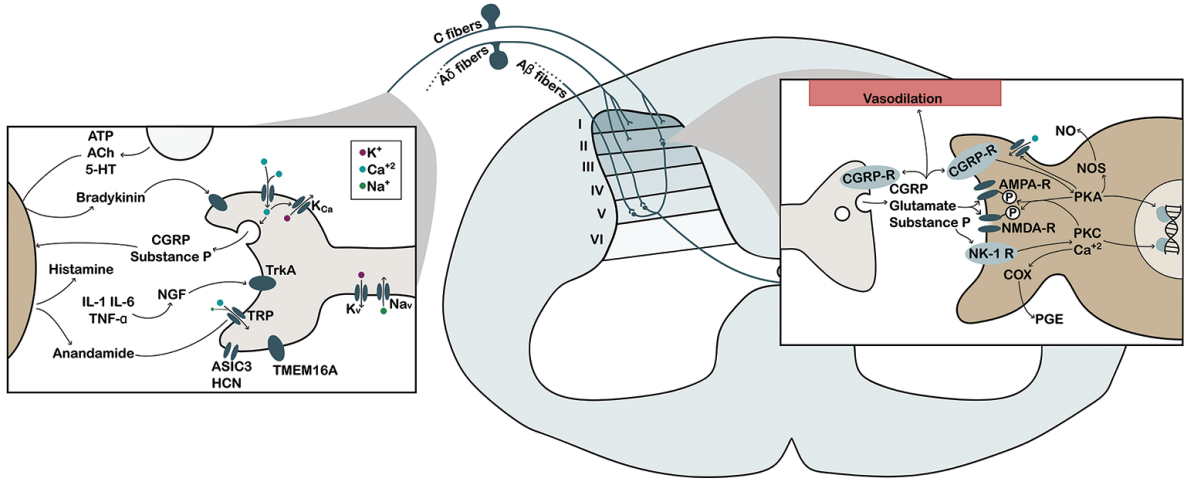

Figure 1. First order nociceptors and their interactions in the periphery and in the dorsal horn. C fibers synapse in laminas I and II whereas Aδ fibers synapse in laminas I and V and outer lamina II. LEFT: Nociceptors react to many stimuli via receptors that are or interact with ion channels that modulate nociceptor excitability, propagate action potentials, and provide negative feedback inhibition at the nerve terminal. During inflammation, peripheral cells release histamine, anandamide, and cytokines that induce growth factors, ATP, ACh, and 5-HT that stimulate production of pronociceptive bradykinins and prostaglandins. In the periphery, release of CGRP and substance P from peptidergic C fibers causes vasodilation, increased vascular permeability, and further degranulation of peripheral cells, thus contributing to neuroinflammation. RIGHT: Release of glutamate in the dorsal horn stimulates NMDA and AMPA receptors. CGRP and substance P binding to their receptors activates PKA and PLC, respectively to increase intracellular calcium and activate PKC. The activated kinases contribute to central sensitization via phosphorylation of membrane proteins and activation of transcription factors. Activation of COX causes increased production of pronociceptive PGE and activation of NOS produces the vasodilator NO. CGRP also exerts vasodilatory effects directly on vasculature. Abbreviations: ACh, acetylcholine; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; ASIC, acid-sensing channels; ATP, adenosine triphosphate; CGRP, calcitonin gene-related peptide; COX, cyclooxygenase; HCN, hyperpolarization-activated cyclic nucleotide-gated channels; 5-HT, serotonin; IL, interleukin; K_{Ca}, calcium-activated potassium channels; K_v, voltage-gated potassium channels; Na_v, voltage-gated sodium channels; N_K1, neurokinin 1; NMDA, *N*-methyl D aspartate; NO, nitric oxide; NOS, nitric oxide synthase; PLC, phospholipase C; PGE, prostaglandin E; PKA, protein kinase A; PKC, protein kinase C; TNF, tumor necrosis factor; TMEM16A, transmembrane member 16A; TRP, transient receptor potential channels.

neurons transmit information to areas including the somatosensory cortices. The spinoreticulothalamic tract contributes to the emotional aspects of and arousal to pain. Second-order neurons synapse in the medullary-pontine reticular formation, then to intralaminar thalamic nuclei that project throughout the cerebral cortex. The spinomesencephalic tract is important in descending pain modulation. The second-order neurons synapse in the periaqueductal gray (PAG), an important mediator of descending pain inhibition.[11]

Central Sensitization

Repetitive C-fiber stimulation produces incremental responses from dorsal horn neurons, whereas Aδ fibers produce a constant response with repetitive firing. Repeated C-fiber activity causes long-term changes in dorsal horn neuron excitability, called central sensitization. The *N*-methyl D aspartate receptors (NMDAR) and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPAR) are glutamate-gated ion channels that seem to be the primary receptors in dorsal horn neurons contributing to central sensitization. NMDAR were originally found important in hippocampal long-term potentiation and are now implicated in long-term potentiation and neuroplasticity at other locations, including the dorsal horn. The initial mechanism of long-term potentiation seems to be the influx of calcium ions via NMDAR and AMPAR that activate second messengers in a positive feedback loop to recruit more NMDAR and AMPAR to the synaptic membrane to strengthen transmission.[12]

Peptidergic C fibers also affect central sensitization by activating second-messenger pathways that modulate neuronal activity to make nociceptors more excitable, change descending pain regulation pathways, and affect activity of transcription factors.[13] In the dorsal horn, subsequent production of nitric oxide (NO) and action of CGRP at presynaptic receptors cause increased neurotransmitter release from the first-order nociceptors. Neuropeptides seem to act via volume transmission, wherein they are released in larger quantities and interact with a greater area of neurons, not just directly at a synapse.[3] CGRP is also a potent vasodilator, with receptors concentrated in the meningeal and mesenteric vasculature. CGRP is important in migraine pathophysiology, because it is the only known peptide released during the headache phase

by trigeminal C fibers and interacts with CGRP receptors on trigeminal Aδ fibers, glial cells, and vasculature. Indeed, CGRP antagonists (small molecule "-gepants" and monoclonal antibodies to CGRP and its receptor) have shown great efficacy in the treatment of migraine and other headache disorders.[14]

Substance P is a tachykinin that binds G protein-linked ion channel receptors (GPCRs), mainly the neurokinin-1 (Nκ-1) receptors. Substance P upregulates expression of Nκ-1 receptors in the dorsal horn. Binding to Nκ-1 receptors activates the protein kinase C (PKC) pathway, initially exciting dorsal horn neurons, likely through decreased conductance of potassium channels. Other downstream effects contribute to central sensitization including PKC phosphorylation of NMDAR, decreased magnesium ion gating of NMDAR, activation of calcium/calmodulin-dependent protein kinase, and production of activating molecules including prostaglandins and NO. Longer-term effects may include activation of the transcription factor, nuclear factor of activated T cells (NFAT), requiring increased intracellular calcium.[3]

Descending Regulation

The many ascending afferents involved in nociception are regulated by interneurons and descending pathways. Many descending pathways regulate nociception with monoamines. Neurons from areas including the cingulate gyrus and PAG stimulate descending serotonergic pathways from the rostral ventromedial medulla (RVM), including the raphe nucleus, and noradrenergic pathways in the dorsal pons, including the locus coeruleus. 5-HT_1 receptors are antinociceptive via inhibition of ascending spinothalamic neurons, interneurons, and primary afferents. In contrast, 5-HT_3 receptors increase nociception by activating primary afferents and ascending spinothalamic tract neurons. 5-HT_2 receptors are also pronociceptive to a lesser extent. Norepinephrine is antinociceptive via interaction with postsynaptic α-1 receptors on inhibitory interneurons and with pre- and postsynaptic α-2 receptors that decrease neurotransmitter release.[15,16] Possibly because of inhibition of norepinephrine and 5-HT uptake, tricyclic antidepressants (TCAs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) have some efficacy treating neuropathic and nociplastic pain syndromes (eg, migraine, diabetic neuropathy, and fibromyalgia, and chronic musculoskeletal pain), increasingly shown to have neuropathic attributes. Adrenergic effects of these antidepressants seem more important for analgesia, considering the lower efficacy of selective serotonin reuptake inhibitors (SSRIs) for pain. Some animal studies suggest these have additional benefits when administered long-term via effects on neuroplasticity.[7]

Descending dopaminergic neurons originate mainly from the A11 nucleus in the posterior hypothalamus and project onto the dorsal horn, which contains dopamine-like receptors ($D_{1\text{-}5}$). D_1-like receptors (D_1 and D_5) are pronociceptive via stimulation of spinothalamic neurons, whereas D_2-like receptors ($D_{2\text{-}4}$) are

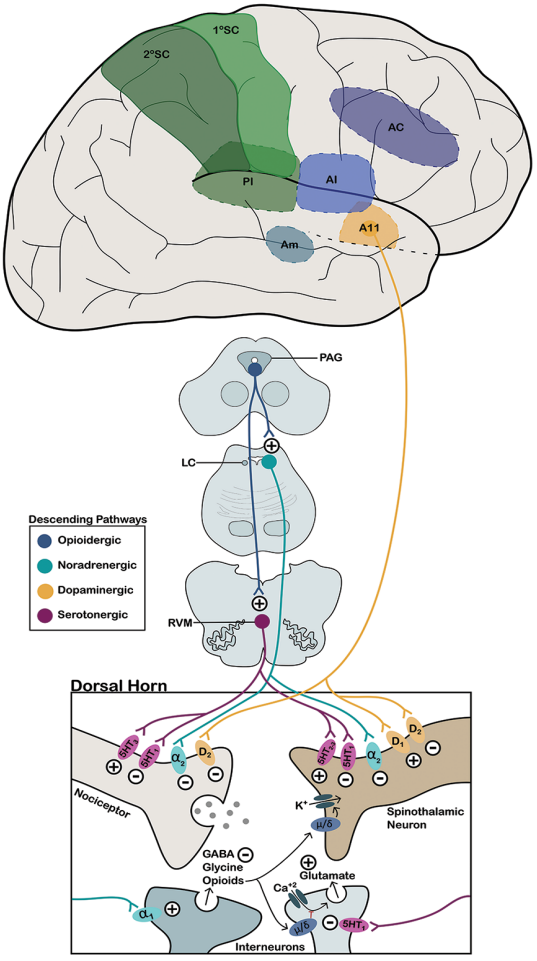

Figure 2. Areas important in sensory-discriminative pain processing include the primary somatosensory cortex (1°SC), secondary somatosensory cortex (2°SC) and posterior insula (PI). Areas important in affective processing are the anterior insula (AI), anterior cingulate cortex (AC) and the limbic system, including the amygdala (Am). Descending pain modulating pathways include opioidergic from the periaqueductal gray (PAG), noradrenergic from the locus coeruleus (LC), dopaminergic from the A11 hypothalamus (A11), and serotonergic from the rostral ventromedial medulla (RVM). INSET: In the dorsal horn, noradrenergic α2, dopaminergic D_2, serotonergic 5-HT_1, and opioidergic μ and δ receptors differentially inhibit afferent nociceptors, ascending spinothalamic neurons, and excitatory interneurons. Noradrenergic α1, dopaminergic D_1, and serotonergic 5-HT_2 and 5-HT_3 receptors differentially activate afferent nociceptors, ascending spinothalamic neurons, and inhibitory interneurons.

antinociceptive through presynaptic inhibition of neurotransmitter release and possible potentiation of opioids.[15,16]

Endogenous opioids including enkephalin, beta-endorphin and dynorphin and their μ, δ, and κ opioid receptors are located throughout the nervous system and are the prominent mechanism of descending pain regulation. These receptors

mainly exert their effects through GPCRs by 1) decreasing calcium influx into the presynaptic terminal to inhibit neurotransmitter release; and 2) increasing potassium conductance in the postsynaptic neurons to hyperpolarize them. Opioid receptors function in many areas (eg, anterior cingulate cortex to control affective pain processing, somatosensory cortex to process discriminative aspects of pain, the hippocampus, thalamus, ventral tegmental area, brainstem, spinal cord, and primary afferents) and effects vary by location—μ receptors in the anterior cingulate cortex inhibit glutaminergic neurons to inhibit affective pain, whereas those in the PAG and nucleus accumbens inhibit GABAergic neurons to increase activity of the descending monoamine pathways. Opioids seem to inhibit affective and somatic responses to pain at lower doses than needed to inhibit the sensation of pain.[17] Different types of nociceptors express various combinations and amounts of opioid receptor classes, indicating some specificity of pain type between receptors. μ and δ receptors are expressed in the dorsal horn by excitatory interneurons and neurons in the anterolateral tract. Other inhibitory interneurons release enkephalin and dynorphin and are activated during peripheral injury. On peripheral nociceptors, inflammation causes upregulation and activation of opioid receptors that are normally inactive.[18] Interestingly, people treated with naloxone had less analgesic placebo effect and less activity in cortical areas responsible for pain modulation than those treated with saline, highlighting the important role endogenous opioids play in internal mechanisms of pain relief.[19]

Processing

Descending modulatory pathways from PAG and RVM are influenced by higher cortical processes (eg, intrinsic fluctuations in attention). The default mode network (DMN) and the salience network are both thought to be important in attention to pain. The DMN involves the posterior cingulate cortex/precuneus, medial prefrontal cortex, lateral parietal lobe, and parts of the medial temporal lobe. The DMN is activated and has more synchronous activity with descending pain pathways when attention is focused away from sensory input. Conversely, the salience network, which includes the anterior insula, midcingulate cortex, temporoparietal junction, and dorsolateral prefrontal cortex, is activated when attention is directed toward pain. Intrinsic attention to pain may contribute to different individual experiences of pain, because individuals with a lower level and variability of connectivity between the DMN and descending pain pathways have higher awareness of pain. Interestingly, people with chronic back pain and migraine were shown to have abnormal functional connectivity (ie, synchronous activity) between descending pain control centers and the DMN and salience network. Areas that influence attention to pain may be therapeutic targets and suggest that behavioral approaches that alter attention to various inputs (eg, cognitive behavioral therapy) may be useful for helping people with chronic pain.[20]

A study looking for a neurologic signature of pain found differential activation of certain brain structures was predictive of pain with high sensitivity and specificity compared with nonpainful warm stimuli, pain anticipation, and pain recall. The signature included increased activity in the bilateral dorsal posterior insula, secondary somatosensory cortex, ventrolateral and medial thalamus, hypothalamus, and dorsal anterior cingulate cortex. This pain signature could also discriminate between pain intensities of heat, but not different intensities of nonpainful warm stimuli. The pain signature was reliably suppressed by both participant-known and hidden infusions of an opioid.[21]

Afferent pain pathways communicate with a variety of cortical and subcortical structures, and certain areas integrate different aspects of pain. The primary and secondary somatosensory and posterior insular cortices are important for sensory-discriminative processing of pain quality, location, and intensity. The anterior cingulate cortex, anterior insular cortex, and limbic system are important for affective-motivational pain, which causes the unpleasant experience of and behavioral responses to pain. Interestingly, acute pain may be transmitted more through the spinothalamic tract to the somatosensory, insular, and anterior cingulate cortices via the thalamus, whereas chronic pain seems to transmit more through other pathways which strongly activate the prefrontal cortex.[22]

Areas of the brain implicated in affective responses to physical pain include the dorsal anterior cingulate cortex and anterior insular cortex. Individuals with lesions in these areas still detect physical pain but are not bothered by it. These brain areas are important not only for nociception but also for processing social rejection. Indeed, study participants randomly assigned to receive daily administration of acetaminophen showed less activity in these areas and reported decreased intensity of daily hurt feelings.[23] The limbic system also processes affective pain responses. The amygdala is important in emotional responses, including aversive learning in which painful stimuli are remembered and trigger a threat response upon re-exposure to that stimulus. Inputs to the amygdala include CGRP-containing peptidergic neurons, which project from the parabrachial nucleus. Lack of these neurons has been shown to eliminate the aversion to previously painful stimuli, while aversion to direct pain remains intact.[24] Although much is yet to be discovered about the cortical and subcortical processing of pain, these pathways help explain clinically observed phenomena regarding the complex reaction to pain and emotional components that affect pain perception.

Conclusion

Among the many challenges of assessing and treating pain is the complex pathophysiology of pain. We have attempted to outline a framework of the known mechanisms of pain and headache. Unlike identifying a pathogen responsible for a

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patient's infection and treating it with the appropriate antibiotic, treatment of pain poses greater difficulty for clinicians. It is unlikely we can assess people in pain and determine the exact mechanism of their complaints. Nevertheless, scientific advances have led to a greater understanding of the mechanisms of pain, which has led to treatments currently in use and active development of new therapies ranging from neuromodulation to new pharmacotherapeutics and recognition of the importance of physical activity and cognitive behavioral approaches in the management of disorders associated with pain and headache. The optimal management of pain and headache is through a multimodal approach that reflects the need to address the complex mechanisms described in this review. ■

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