THE NEUROBIOLOGY OF NOCICEPTIVE AND ANTI-NOCICEPTIVE SYSTEMS

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Pain is both a sensory event of the peripheral and central nervous systems and an experience that arises from, and reciprocally can affect processes of higher consciousness. Alterations in peripheral and central neuraxes can lead to sensitization, structural modification and long-term potentiation that can overcome modulatory influence(s) and change the non-linear adaptability of these systems to a progressively linear, pathologic state with a diverse constellation of clinical signs and symptoms.

Recent progress in molecular biology, neurochemistry and neuroanatomy has led to significant advancement in understanding the interactive roles of these heterogeneous systems in mediating and modulating various types of pain. This review concisely provides an overview of the structure and function of these substrates. As we reach the midpoint in a decade marked by pain control and research, such knowledge is critical to further both a more comprehensive appreciation of the phenomenon that is pain, and the development of therapeutic interventions that are innovative and effective.

Keywords: Pain, analgesia, neuroanatomy, neurobiology, neuropharmacology

Transduction of Noxious Stimuli

In cutaneous, muscle and visceral tissues, transduction of high threshold (noxious) chemical, mechanical and/or thermal stimuli to electrophysiological activity occurs at specialized free nerve endings of nocisponsive primary afferents. The transductive mechanism involves activation of cationic channels on free nerve endings directly by biophysical properties of the high threshold noxious stimuli and indirectly by chemical changes in the local micro and macro environment produced by such stimuli, and trauma. Thermal nociceptive transduction is mediated by vanilloid-type receptor-cationic channel(s). The vanilloid receptor-1 (TRPV1) responds to noxious heat (>45°C) and is capsaicin-sensitive. A second type, the vanilloid receptor-like protein-1 (TRPV2) is capsaicin-insensitive and has a higher thermal threshold of approximately 52°C. The cold- and menthol-receptor-1 (CMR-1/T8) responds to noxious cold (8°-25°C) and menthol. Both hot- and cold-responsive channels react to thermal change by increasing mono- or divalent cationic flux, leading to membrane depolarization and transduction (1, 2).

High threshold compressive or tensile mechanical input engages a non-specific cationic channel by distorting collagenous bridging elements between the membrane of free nerve endings and the surrounding tissue matrix. With mechanical alteration of the receptive field of the neural membrane, changes in channel configuration produce inward Na+, K+ and/or Ca++ currents (3). The nociceptor potential is graded, membrane polarity is intensity- and temporally-dependent. At the Na+ threshold, voltage-gated Na+ channels are activated, propagating depolarization along the nociceptor membrane. Both Na+ and Ca++ influx lead to the release of Ca++ from intracellular stores, increasing Ca++ concentrations to engage signaling systems mediating short-term functional changes that may lead to leftward shifts in nociceptive threshold. Also, long term changes in Ca++-dependent intracellular signaling mechanisms alter early and late-phase transcription to modify translation, and protein synthesis alters neuronal microstructure. Taken together these changes contribute to sensitization of peripheral afferents (4).

High threshold input can disrupt neural and non-neural membranes to release fatty acids as well as mono and divalent cations. Liberated free fatty acids are catalyzed by phospholipase-A2 to pro-
duce arachidonic acid; increased concentration of arachidonic acid induces the isoenzyme cyclo-oxygenase-2 (COX-2) to accelerate prostaglandin formation, with “downstream” production of prostaglandin synthase-generated prostaglandin E2. Prostaglandin-E2 acts at PGE-2 receptors on nociceptors to increase adenyl cyclase, elevating cyclic adenosine monophosphate (cAMP) to engage specific protein kinases. Both protein kinase A and C phosphorylate prostanoid, kinin, and amine receptors and ion channels, affect their respective sensitivity to ligands and ionic concentrations. This can enhance the responsivity of affected primary afferents to both noxious stimuli (i.e. hyperpathia) and non-noxious stimuli (i.e. allodynia) (5) (Table 1).

### Table 1. Algogenic stimuli and substrate(s) mediating transduction

<table>
<thead>
<tr>
<th>Stimulus</th>
<th>Substrate</th>
<th>Channel</th>
<th>Sensitivity</th>
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<tbody>
<tr>
<td>H+ ion</td>
<td>TRPV1/V1 receptor channel</td>
<td>Na+, Ca++ influx</td>
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<tr>
<td>Protons</td>
<td>Acid- sensitive ion channel (ASIC)</td>
<td>Na+ influx</td>
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<tr>
<td>Noxious Heat &gt; 45°C (and capsaicin)</td>
<td>TRPV1/V1</td>
<td>Na+, Ca++ influx</td>
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<tr>
<td>Noxious Heat &gt; 53°C (capsaicin insensitive)</td>
<td>TRPV2</td>
<td>Na+, Ca++ influx</td>
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<tr>
<td>Noxious Cold 8°-25°C (and menthol)</td>
<td>CMR1/trpM8</td>
<td>Na+, K+, Ca++ influx</td>
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<tr>
<td>Mechanical Distortion</td>
<td>Non-selective cation channel</td>
<td>Na+, K+, Ca++ influx</td>
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<tr>
<td>BDNF</td>
<td>TrkB receptor</td>
<td>MAPK activation- transcription effects</td>
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<tr>
<td>Prostaglandin- E2</td>
<td>Prostanoid receptor</td>
<td>Metabotropic activation of protein kinase</td>
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<td>Serotonin (5-HT)</td>
<td>5-HT1 receptor</td>
<td>Na+ influx</td>
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<td></td>
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<td>NK-1 receptor sensitization</td>
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<td></td>
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<td>NO production</td>
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<tr>
<td>Adenosine</td>
<td>A2 purinoreceptor</td>
<td>Sensitization of Na+ channels</td>
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<tr>
<td>ATP</td>
<td>PTX3 receptor</td>
<td>Sensitization of Na+ channels</td>
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<tr>
<td>Glutamate</td>
<td>AMPA receptor</td>
<td>Na+ influx</td>
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<td></td>
<td>NMDA receptor (GluR)</td>
<td>Na+ influx</td>
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<td></td>
<td>mGlu receptor</td>
<td>Ca++ influx</td>
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<td>Phospholipase-C-induced rise in intracellular Ca++ Protein kinase-C phosphorylation/ sensitization of trkB</td>
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<tr>
<td>Bradykinin</td>
<td>Bradykinin B2 receptor</td>
<td>Cationic influx</td>
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**Transmission from the Periphery to the Spinal Cord**

Upon transduction of the high threshold stimuli, the nociceptive signal is transmitted by primary nociceptive afferents via Na+-dependent depolarization mediated by several isoforms of Na+ channels, most notably the nociceptor-specific Na,1.8 and Na,1.9 channels. Under normal conditions the majority of these channels are of the tetrodotoxin (TTX)-sensitive type, however, neural insult, inflammation, and exposure to algogenic substances cause increased expression of a TTX-resistant (TTX-R) isoform, which may subserve lowered threshold Na+ conductance (6).

It is now well known that multiple small-fiber afferents can transmit nociception, based upon their expression of transductive receptors and TTX-R type Na+ channels. However, A-delta and C-fibers are still regarded as the principle primary afferents that distinctly subtend noxious input (high threshold mechanical, thermal, polymodal) and their differential activity contributes to the respective sensory qualities of fast and slow pain.

**A-Delta Fibers**

Type I and II A-delta fibers are small (1-5 um in diameter) myelinated, rapidly conducting (5-30 m/sec) neurons. The conduction rate is correlated to the initial sensation of pain, “first pain,” as sharp, localized and subjectively punctuate. A-delta fibers have small receptive fields and specific high threshold ion channels that are activated by high intensity thermal or mechanical input. Type II A-delta thermo-responsive fibers are sensitive to capsaicin and respond to noxious heat of 40-45°C. Response increases with temperature elevation, with asymptotic response at 53°C. A second population, Type I fibers, are responsive to higher temperatures (52-56°C) and are capsaicin-insensitive. The responses of these heat-sensitive A-delta fibers subserve the rapid, painful reaction to first exposure of noxious heat and the ability to discriminate thermal (nociceptive) sensation according to intensity. A-delta cold afferents maximally respond to temperatures of approximately 8°C and show progressive activity to temperatures less than 25°C (7).
tized by, and subsequently co-responsive to (intense) heat. Sensitization of these mechanoreceptive A-delta fibers to thermal stimulation may subserve patterns of hyperalgesia following heat or burn injury (8).

C- and C-like Fibers
C-fibers constitute the majority of cutaneous nociceptive innervation and are small (0.25-1.5 um diameter), unmyelinated afferents with slower conduction (0.5-2 m/sec) and larger receptive fields than A-delta fibers. These characteristics contribute to “second pain,” the poorly-localized burning, gnawing sensation that is qualitatively distinct from “first” or fast pain. C-fibers are polymodal, activated by mechanical, thermal and/or chemical stimuli. The chemical substances that stimulate C-fibers are products of cell disruption, the inflammatory cascade and immunological mediators (9); free H+ sensitizes the TRPV1 vanilloid receptor on C-fiber endings to evoke Na+ and Ca++ influx. Protons act at acid-sensitive ion channels to induce inward Na+ current. ATP and ATP-derived adenosine acts at P2X and A1 purinoreceptors, respectively to sensitize Na+ channels, increase Na+ conductance and evoke depolarization. Such chemical stimulation may occur following thermal or mechanical insult and produces a sensitizing leftward shift in C-fiber response threshold. These sensitized C-fibers can be activated by non-noxious, low intensity stimulation that accounts, in part, for the second pain and/or hyperalgesia as a consequence of inflammation (10).

C-fibers, and some A-delta fibers also innervate the intrafibril matrix and areas proximal to the vascular walls of muscle tissue, as well as musculo-tendinous insertion zones and tendons. Polymodal C-afferents respond to both direct mechanical excessive stretch, torsion or hyper-compression – and to substances resulting from prolonged anaerobic metabolism and ischemia. Muscular C-fibers are activated by H+ ions of the acidic post-metabolic environment and by inflammatory mediators following exercise induced micro- or macro-trauma, microedema and heat. The stretch reflex does not normally activate intramuscular C-fibers, however, under ischemic conditions C-fibers may be sensitized to respond to myofibrillar contraction and stretch within the physiologic range. Ischemia increases the concentration of free adenosine which activates A2 receptor-linked G-protein-modulation of Na+ channel threshold(s). Such sensitization appears to subserve the diffuse pain that occurs during passive and active articulation of skeletal muscle that has been over-exerted or subjected to mechanical or ischemic insult (11, 12).

There is considerable C-fiber innervation of the viscera, although polymodal A-delta fibers are significantly abundant in the testes, structures surrounding the heart, and a small unmyelinated C-like fiber has been described in the lung parenchyma (13). The nociceptive afferent innervation of visceral structures is more sparse than in cutaneous or muscular tissues; there is also considerable diffusion of visceral afferent input within the spinal dorsal horn. Sensitization by chemical mediators of the inflammatory cascade or sympathetic outflow is required for the sustained firing of the visceral nociceptive afferents necessary to activate second order spinal afferents and transmit the nociceptive signal. The initial sensation and perception of visceral pain is somewhat vague; intensity and localization increase as a function of increased discharge frequency of primary afferents and summated transmission at second-order spinal neurons. Visceral nociceptive afferents are anatomically co-localized with somatocutaneous afferents in the entry zone of the dorsal root ganglia and within afferent synaptic fields of the dorsal horn. Increased transmission of visceral afferents at the dorsal root and horn zones where their input overlaps with somatocutaneous afferents causes signal convergence at second-order neurons and may subserve the somatic referral pattern that frequently accompanies visceral pain (14).

Also, there is often co-localization of visceral nociceptive and sympathetic (efferent) neurons. Stimulation of sympathetic fibers by ephaptic transmission from adjacent nociceptive afferents or by direct co-stimulation of sympathetic nerves following peripheral insult can increase synthesis and membrane expression of high-affinity adrenergic receptors, enhancing peripheral adrenergic sensitivity, sympathetically-maintained pain and peripheral autonomic dysregulation. Noxious stimulation of visceral structures can thus excite sympathetic neurons to induce efferent sympathetic outflow, producing altered autonomic tone and sympathetically mediated hyperalgesia. Sympathetic alterations are also observed in certain cutaneous and muscular pain syndromes (15) and are contributory to the vaso- and sudomotor characteristics of complex regional pain syndromes (CRPS) (Table 2).

The Neurochemical Basis of Pain Transmission in the Dorsal Horn

The majority of nociceptive primary afferent fibers project to the superficial dorsal horn, although a small number project to the ventral spinal cord. In the dorsal horn, A-delta and C-fibers synapse upon second order spinal neurons in laminae I, II, Ila, and V, from which originate the ascending nociceptive pathways. A-delta fibers terminate in laminae I, II and Ila; C-fibers terminate laminae II, Ila and V.

Glutamate is the principal excitatory transmitter at the synapse between primary afferent nociceptors and dorsal horn cells. Glutamate initially binds to the alpha-amino-3-hydroxy-5-methyl-isoxazole-4 propionic acid (AMPA) receptor. Glutamate-activation of the AMPA receptor induces a ligand-gated Na+ current to produce rapid depolarization. Sustained Na+ flux activates the N-methyl-D-aspartate (NMDA) receptor, by voltage-dependent displacement of Mg+ from the NMDA receptor, releasing it from an inaccessible configuration to an active site with subsequent high affinity for glutamate.

The AMPA receptor is a heteromeric composite of multiple potential glutamate binding sites (GluR) that regulate a fast-on, slow-off, Ca++ ionophore. Additionally, one or more of the eight metabotropic, G-protein-coupled glutamate receptors (mGluR) exist in nociceptive neurons. Activation of the mGluR induces a specific phospholipase-C to engage inositol trisphosphate (IP3)-mediated release of Ca++ from intracellular stores. Increased intracellular Ca++ activates Ca++-sensitive protein kinase-C (PKC) to phosphorylate inactive and sub-membrane fractions of AMPA, NMDA, GluR and mGlu receptors, altering the sensitivity of these receptors and affecting their shutting to active zones on the neural membrane. Metabotropic mGluRs can also engage diacylglycerol (DAG) to produce PKC-mediated phosphorylation of the tyrosine kinase-B (trkB) receptor for brain-derived
afferents

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DAG-dependent activation of protein kinase C-pro-tein-medi-cated depolarization and subs-P acts at NK-1 receptors to induce a sensitive to lower subs-P concentrations. In high affinity NK-1 receptors that are nin-2 (NK-2) receptors, and subse-quently, subs-P initially binds to neurok-inin, substance-P (subs-P). Post-synap-tic activity causes the release of the tachyki-nics may alter the synaptic “state” and subserve acute and intermediate sensitiza-tion of second-order afferents. Prolonged activation of newly synthesized glutamate receptors can affect genomic elements to produce durable change in the neuronal microstructure leading to plasticity and long-term potentiation (LTP) of neuronal function and synaptic microstructure of cells receiving and transmitting nociceptive input (18, 19).

These mechanisms of receptor dynamics may alter the synaptic “state” and subserve acute and intermediate sensitization of second-order afferents. Prolonged activation of newly synthesized glutamate receptors can affect genomic elements to produce durable change in the neuronal microstructure leading to plasticity and long-term potentiation (LTP) of neuronal function and synaptic microstructure of cells receiving and transmitting nociceptive input (18, 19).

Sensitized C-fiber afferents retrogradely release subs-P, acting at NK-1 receptors on mast cells to induce degranulation of the pro-inflammatory chemicals histamine and serotonin (5-HT). C-afferents also release calcitonin gene related peptide (CGRP); CGRP activates the induced isoenzyme nitric oxide synthase (iNOS) to enhance production of nitric oxide (NO) and increase peripheral vasodilation (10). The effects of histamine, 5-HT, subs-P, and CGRP are synergistic. In peripheral tissue(s), free 5-HT acts at 5-HT3 receptors on C-fiber terminals to directly induce a fast Na+-dependent depo-larization, sensitizes NK-1 receptors to subs-P, and evokes co-release of CGRP to increase iNOS production, thereby perpetuating the cycle of C-fiber-mediated neurogenic inflammation and pain (20, 21).

Table 2. Neurochemical and physiologic properties of primary nociceptive afferents

<table>
<thead>
<tr>
<th>Type</th>
<th>Anatomy</th>
<th>Physiologic Properties</th>
<th>Neuro Chemistry</th>
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<tbody>
<tr>
<td></td>
<td>Free endings</td>
<td></td>
<td>Glutamate</td>
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<tr>
<td></td>
<td>Myelinated</td>
<td>High threshold</td>
<td>Subs- P</td>
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<td></td>
<td>1-5 µm fiber diameter</td>
<td>Mechanical</td>
<td>CGRP</td>
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<td></td>
<td>Punctate fields</td>
<td>Thermal</td>
<td>VIP</td>
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<td></td>
<td></td>
<td>(&gt;45°, &gt;53° C)</td>
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<td></td>
<td></td>
<td>(&lt;25°C)</td>
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<tr>
<td></td>
<td></td>
<td>Slow</td>
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<tr>
<td></td>
<td></td>
<td>0.5-2 m/sec conduction</td>
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<td>STIMULUS</td>
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<td>First pain</td>
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<tr>
<td></td>
<td></td>
<td>Poorly localized</td>
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<tr>
<td></td>
<td></td>
<td>Sensitized, Cross-Sensi-tized</td>
<td>Post-synaptic activation of AMPA receptors</td>
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<td></td>
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<td></td>
<td>Post- synaptic activation of NMDA receptors</td>
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<td>Potentiated NK-1 receptor activation</td>
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<td></td>
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<td>May induce neural plasticity</td>
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</table>

**Dorsal Horn Afferents**

In the dorsal horn, A-delta and C-fibers synapse upon WDR and NS neurons that spatially and temporally transform afferent input(s). While a small percentage of the axons from these neurons ascend ipsilaterally within the cord, most project contralaterally to form the spinothalamic tract(s) (STT) and ascend in the anterolateral quadrant.

WDR neurons are found in progressively increasing numbers from laminae I, II, V to VI. These neurons receive input both from low threshold A-alpha and A-beta non-nociceptive afferents as well as A-delta and C-fibers, with the majority of nociceptive fiber input in lamina V. The WDR units of laminae I and II are responsive to non-noxious thermal and gentle mechanical input. WDR cells of lamina V have large receptive fields with limited, discrete areas excited by non-noxious input and broad zones that are highly responsive to high threshold stimulation. These receptive field properties function in stimulus intensity discrimination with different stimulus intensities activating distinct receptive field zones in populations of WDR neurons. The slight phase difference in temporal activation produces differing responses in these groups of WDR cells. As greater numbers of WDR neurons become stimulated there is an increase in both the spatial and temporal summation of their responses, resulting in amplification of the pain signal (22).

Nociceptive specific (NS) neurons are concentrated in laminae I and II, with fewer in lamina V. NS neurons are driven by A-delta and C-fiber input, and have small, center-surround receptive fields in which the central region is excited by high intensity stimuli, while the outer region appears to be inhibited by non-noxious input. These receptive field properties render the NS cell maximally responsive to punctate, high threshold inputs and subserves its function in localization and discrimination of noxious stimuli (22, 23).

Both WDR and NS fiber activity contribute to the unique spatial and temporal qualities of pain. NS neurons can remain sensitized following repetitive noxious input and WDR neurons exhibit prolonged after-responses (e.g., “wind-up”) generated from the extent and frequency of primary nociceptive afferent input, thus intensifying and continuing nociceptive transmission and sensation(s) (23) (Table 3).
Spinothalamic Tracts
While a minority of WDR and NS neurons remain ipsilateral and ascend in the ventrolateral quadrant, most project contralaterally to form the STT and ascend in the anterolateral column. Axons from neurons in laminae I and II are somewhat anatomically separate from those of laminae IIa and V, providing a degree of anatomic and functional segregation of the fibers that form the neo-spinothalamic tract (NSTT) and paleo-spino-
thalamic tract (PSTT), respectively. The NSTT and PSTT are both relatively specific for pain transmission, yet there are distinctions in the type of nociceptive information conveyed along these pathways. The NSTT is composed of NS fibers from laminae I that project to the parabulbar nucleus and fibers from laminae I and II that terminate in the ventroposterior lateral (VPL) nucleus of the thalamus. The parabulbar projection subserves arousal and autonomic responses to pain via secondary connections to hypothalamic and amygdalar neuraxes, while VPLthalamic projections subsume transmission of stimulus modality and localization, although this is in no way exclusive to other stimulus parameters (24).

The PSTT is predominantly comprised of axons of WDR neurons from lamina Ia and V, with only a smaller number of constituent NS fibers. The heterogeneous response characteristics of WDR cells to noxious and non-noxious input contributes to the transmission of some non-nociceptive signals by the PSTT. WDR neurons progressively summate after-responses to nociceptive input that supersede weaker volleys driven by non-nociceptive afferent activity. These properties contribute to stimulus intensity discrimination and to the characteristic “mixed” sensations that frequently accompany “second” and persistent pain such as ache, itch, tingling, etc. (25).

The PSTT projects to the parabulbar nucleus and to structures of the rostroventral medulla, caudal pons and midbrain that subserves bulbospinal pain modulation and centrifugal analgesia.

Spinoreticular pathways project to the serotonergic raphe nuclei and noradrenergic magnocellular nuclei of the rostroventral medulla and caudal pons, respectively. Spinotectal pathways project to the periaqueductal and periventricular gray (PAG/PVG) regions of the midbrain. Ascending projections from these sites link spinal and corticobulbar neuraxes to mediate perceptual, cognitive and emotional aspects of pain. Thalamic targets of the PSTT are more diffuse, with projections to the centro-median parafascicular complex, intralaminal, laterodorsal and mediodorsal nuclei (25, 26).

**Brainstem Systems**

Specific cells of the brainstem (i.e., “on,” “off” and “neutral” cells) are differentially responsive to PSTT input driven by noxious stimulation. “On” cells are excited by nociceptive input from the PSTT and engage parabulbar, hypothalamic, circumventricular, insular and septo-hippocampal pathways, subserving arousal and amnesic reactions to pain. Some 5-HT neurons of the raphe nucleus may be “on” cells that function in descending bulbospinal analgesia, and may participate in nociceptive facilitation that occurs in chronic inflammation and neuropathic pain states. “Off” cells hyperpolarize in response to PSTT activation and reduce the transmission of nociceptive volleys at the brainstem. The summative actions of these cells are dependent upon the duration, intensity, and type of noxious input contributing to inhibitory or facilitatory patterns of pain modulation (27).

PSTT projections to distinct nuclei of the brainstem possibly subserve some stimulus-specific involvement of descending serotonin (5-HT) and noradrenergic (NE) systems. Thermal and chemical/inflammatory pain appears to engage raphe-spinal 5-HT circuitry, while mechanical input produces greater activation of magnocellular-spinal NE neuraxes. It is not clear whether these distinctions are truly stimulus-specific or reflect different bulbospinal responses to stimulus intensity, duration, or both (28). While it is well known that these systems function in pain inhibition (vide infra), recent evidence supports the involvement of the raphe-spinal 5-HT system in pain facilitation (29).

Serotonin acts through heterogeneous 5-HT1, 5-HT2 and 5-HT3 found post-synaptically on primary and secondary afferents, and interneurons in superficial and deep layers of the dorsal horn. The action of 5-HT at post-synaptic 5-HT1 and/or 5-HT2 receptors directly inhibits primary and/or secondary cells to produce analgesia. Raphe-spinal 5-HT can also indirectly modulate pain by acting at excitatory 5-HT3 receptors on inhibitory interneurons to evoke the release of inhibitory neurotransmitters such as GABA, glycine, enkephalin, and dynorphin. Under normal conditions and perhaps during acute pain, there is limited expression of 5-HT3 receptors and a relative “tone” of excitation and inhibition is maintained within the pool of spinal nociceptive neurons. However, more durable, intense pain, as well as peripheral inflammation and neural insult, appear to evoke up-regulation of 5-HT3 sites on both interneurons and small-diameter, nociceptive afferents of the superficial lamina. In the former case, this may represent 5-HT3 receptor sensitization to progressively rising concentration of 5-HT released from the terminals of descending raphe-spinal neurons in response to direct PSTT stimulation (30).

Expression of 5-HT3 receptors on lamina I nociceptive cells appears to involve an NK-1 receptor-dependent mechanism in which sub-P activation of NK-1 receptors initiates transcription, translation and/or commitment of a sub-membrane fraction of 5-HT3 receptors that then mediate an excitatory response to raphe-spinal 5-HT. Hyper-excitation of interneurons results in debilitating turnover of inhibitory neurotransmitters; 5-HT3 receptor-mediated excitation of nociceptive
cells of the cord “reverse” the characteristic inhibitory effect of the raphe-spinal 5-HT system. Taken together, these actions lead to nociceptive facilitation and sensations of pain in excess of the level of organic insult that is often observed in inflammatory, neuropathic or chronic pain states (29).

**The Midbrain**

The PSTT projects to and activates the PAG directly via interneurons from the brainstem. The PAG is somatotopically organized such that the posterior PAG receives PSTT fibers of the caudal cord, while PSTT fibers from the rostral cord project to the anterior PAG. In addition to being a primary site of centrifugal pain control, the PAG also subservesafferent processing of the pain signal; projections from the PAG to the hypothalamus and structures of the forebrain such as the septal nuclei and amygdala, elicit arousal and behavioral activation that have aversive affective content and expression (31). These responses function in pain conditioning by activating cognitive circuitry of the mammillo-thalamic tract, anterior thalamic nucleus, cingulatum, and regions of the hippocampus to act in synergy with the reticular system, cingulate gyrus, insula and orbito- and frontal cortices.

**The Thalamus**

NSTT neurons project to the caudal ventroposterior lateral nucleus (VPLc) and are arranged in somatotopic columns. Thalamic neurons within these columns retain many of the response characteristics of WDR and NS cells, and summate responses as a function of stimulus frequency and intensity. Spatial and temporal summation prolong thalamic cell discharge. Such serial processing of nociceptive input may contribute to the qualitative and quantitative characteristics of pain sensation (32).

The PSTT projects to the intralaminar, dorsal centralis lateralis and mediodorsal nuclei, and the majority of these thalamic neurons are responsive to input from both nociceptive and non-nociceptive cutaneous and visceral afferents. The somatotopic organization of intralaminar neurons is more diffuse, and these cells project to the S-II somatosensory associative cortex, anterior and posterior cingulate gyrus and amygdala, to synergistically mediate aversive and avoidant responses to pain (Fig. 2) (33).

**Thalamo-Cortical Projections and the Afferent Role of the Cortex**

Thalamo-cortical fibers from the VPLc primarily project to the S-I sensory cortex, with a lesser projection to S-II. Fibers from the intralaminar, lateral, and mediodorsal nuclei activated by the PSTT project bilaterally to S-II, although a small number project to S-I. Thalamic somatotopic organization is retained in S-I, and (albeit somewhat less) in S-II, with cortical regions arranged in vertical domains. Only a small percentage of each column is nociceptive neurons; the majority of nociceptive input from the thalamus is concentrated in deeper layers of the cortical columns, while superficial cortical layers receive non-nociceptive thalamic input. The distribution of input from both non-nociceptive and nociceptive afferents in a given column underlies the cortical “assemblage” of neural signals to create the subject sensory (34).

The unique qualities of the duration, intensity, and modality of the pain signal reflect progressive transformation of hierarchical afferent input through the contributory neuraxis.

Projections from S-II to the anterior cingulate (via the insula) and to the posterior cingulate play a role in pain sensation and pain-related behavioral responses (e.g., arousal, nociceptive reactions). Projections from the cingulate to hypothalamic nuclei mediate neuroendocrine and autonomic responses to pain and may also engage non-opioid, hormonally-mediated analgesia. Efferent projections from the anterior cingulate to the caudate, putamen, and nucleus accumbens are involved in the motor responses to pain (35).

The involvement of dopaminergic (DA) pathways from both the ventral tegmental area (VTA) and substantia nigra pars compacta (SNpc) have been described in cognitive and motoric dimensions of pain. Acting through heterogeneous post-synaptic DA receptors, this meso-limbic DA loop functions in negative reinforcement emotional and motor conditioning effects to aversive stimuli, and may subserve certain stereotypic behaviors of both acute and chronic pain states (36).

Pathways from the hippocampus, subicular complex, entorhinal cortex and posterior cingulum further mediate emotional, memory and expectational domains of pain. The lateral dorsal thalamic nucleus and amygdala, together with efferents from the lateral prefrontal, infero-, medio-temporal and infero-parietal cortices mediate higher order cognitive dimensions such as expectation and associative value of pain (37, 38).

Hierarchic neural processing expands nociceptive sense data into consciousness of internal state, external circumstance, memory and affective factors that have both subjective and ontologic meaning to the pain sufferer. Thus, the phenomenologic experience of pain may vary widely for each individual as a result of cortico-limbic processing of complex external and internal stimuli, association(s) to prior circumstance(s) and even socio-cultural contexts. It is likely that “pain” as an experience, is both a sensory event reflecting activation of afferent pathways and a process of consciousness arising from alterations of multiple domains of brain state(s) (Fig. 2).

**Anti-nociceptive Systems**

**Spinal Pain Modulation**

Inhibitory interneurons in laminae I and V of the dorsal horn receive collaterals from A-delta and C-fibers. These interneurons synapse upon primary afferents and second-order WDR and NS cells within a horizontal segment of the cord, although some interneurons project trans-segmentally. The pattern of primary afferent firing can activate these spinal interneurons to exert recurrent inhibition or suppress firing of post-synaptic second-order cells.

These interneurons release GABA, glycine, the opioids dynorphin, leucine and methionine-enkephalin and endogenous cannabinoids. GABA acts at postsynaptic GABA<sub>A</sub> receptors on primary and second-order afferents to induce a slow, chloride anionic hyperpolarizing current; it acts at post-synaptic GABA<sub>B</sub> receptors to metabotropically initiate K<sup>-</sup> mediated hyperpolarization. Dynorphin acts at post-synaptic kappa/OR2 receptors that are negatively coupled to N-type Ca<sup>2+</sup> channels. The dynorphin-activated kappa/OR2 receptor undergoes conformational change, closing the Ca<sup>2+</sup> channel and producing a gradual hyperpolarization. Leu- and met-enkephalin act at both

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delta/or1 and mu/or3 opioid receptors to activate G-protein-mediated kinases, phosphorylate K+ channels and increase K+ influx to produce a hyperpolarizing current. The amino acid glycine may be released or co-released from GABA and dynorphin interneurons. Glycine acts at the glycine receptor, an ionotropic Cl-ionophore, and induces membrane hyperpolarization and post-synaptic inhibition (39). Prostaglandins, specifically PGE2 can antagonize the glycine recep-

**Fig. 2.** Schematic of spinothalamic and thalamo-cortical pathways mediating sensory and cognitive dimensions of pain. The PSTT projects to intralaminar and medial thalamic nuclei. Projections from these nuclei to the anterior cingulate gyrus function in affective dimensions of pain. The anterior cingulate also receives input from the posterior cingulate, SII associative cortex and hippocampus. The PSTT projects to the parabrachial nucleus (nPB) to activate the amygdala and hypothalamus, to mediate arousal and autonomic responses to pain. The NSTT projects to the VPLc thalamic nucleus. Thalamocortical pathways from VPLc project to S1 and SII to mediate sensory discriminative aspects of pain. S1 and SII and the SII-insular-cingulate pathways function in cognitive and emotional dimensions of pain.
tor, thereby reducing the interneuronal pain modulation and producing a trend toward pain facilitation that is characteristic in neurogenic inflammatory conditions. The endogenous cannabinoids, anandamide and 2-arachidonoylglycerol, act at type-1 cannabinoid (CB-1) receptors on second-order neurons in the dorsal root ganglia and superficial laminae, to produce a slow hyperpolarization. Additionally, CB-1 receptors are found in cortical and sub-cortical limbic areas where anandamide and exogenous cannabis act to modulate pain sensation and suppress arousal and aversive behaviors associated with pain. However, it has recently been shown that at higher concentrations may sensitize primary afferent TRPV (vanilloid) receptors and TTX-resistant Na⁺ channels to facilitate nociceptive responses (40) (Fig. 3).

Bulbospinal Analgesia

The PSTT projects to the raphe nuclei the sub-groups of the nucleus raphe magnus (NRM) – of the rostroventral medulla (RVM) and the magnocellular nuclei (RMC: the nuclei reticularis gigantocellularis and reticularis paragigantocellularis) of the caudal pons/RVM. The NRM and RMC receive both afferent input from the PSTT and efferent input from the PAG and that can drive systems of the brainstem nuclei to produce bulbospinal and/or centrifugal analgesia, respectively (41). Inhibitory and excitatory connections in the brainstem determine the relative participation or co-participation of the NRM and RMC in modulating nociception.
pain of different intensities, duration, and modalities (29).

Projections from the NRM and RMC descend in the spinal dorsolateral funiculi and form polysynaptic contacts with popula-
tions of spinal interneurons as well as mono-synaptic contact with second-order and primary afferent neurons in laminae I, II and V. The projection of NRM and RMC fibers to groups of thermo-, mecha-
nociceptive afferents and/or their WDR and NS target cells may affect stim-
ulus-specific patterns of anti-nocicep-
tion mediated by 5-HT or NE bulbospinal pathways (28).

Midbrain-Centrifugal Analgesia

Afferent input from the PSTT and ef-
ferent projections from the cingulate gy-
rus, as well as nuclei of the limbic fore-
brain and hypothalamus activate endor-
phin-, enkephalin- and orphanin-con-
taining neurons of the PAG. Projections from the PAG to the brainstem are both inhibitory and excitatory. Opioids from the PAG act at post-synaptic mu/OR3 re-
ceptors to suppress GABAergic interneu-
rons of the midline brainstem, disinhibi-
ting the tonic and burst activity of de-
scending 5-HT tracts of the raphe-spinal 
system and descending NE from the RMC (42). In contrast, a glutamate-me-
diated pathway from the PAG can excite populations of brainstem “on” and “off” cells to directly engage NRM and/or RMC systems to modulate STT activity. The ac-
tivity of these pathways seems to be reli-
ant upon the intensity of noxious input – milder pain evokes low-level glutamate stimulation of brainstem nuclei while more intense or durable pain engages the PAG in centrifugal suppression of the STT through disinhibition of bulbospinal pathways (41). Additionally, opioids from the PAG/PVG may be released into the ce-
rebrospinal fluid (CSF) and act at popu-
lations of delta/OR1 and mu/OR3 recep-
tors on primary, second-order, and inter-
neurons of the spinal cord to inhibit pain transmission (41, 42) (Fig. 4, Table 4).

Cortical Pain Modulation

Neurons of the sensory cortex can directly inhibit thalamo-cortical projec-
tions arising from the STT; such corti-
co-thalamic inhibition of the non-noci-
ceptive medial lemniscal tract can also occur. Such inhibition increases asymp-
totically with thalamo-cortical input that is rapidly temporally- and spatially-sum-
mating, acting as high band-pass filter for nociceptive information. Cortical neu-
rons can also excite both thalamo-cortical and STT fibers to up-modulate “filtered” information. This compensates for differ-
ent response characteristics between thal-
mamic projections and their target corti-
nal neurons, augments the response func-
tion and enhances the signal:noise ratio of thalamically-driven cortical circuits that function in pain localization and discrimi-
nation (43).

Fibers from the frontal, pre-frontal, and orbital cortex can engage limbic cir-
cuits of the amygdala, septal nuclei, and hypothalamus to modulate nocicep-
tion and pain perception. This latter point is of particular interest in that imaging studies have shown the involvement of the lateral prefrontal cortex in placebo and “expecta-
tional” analgesia. This site may also acti-
uate limbic, or PAG-descending modular-
ary components, to play a role in the en-
gagement and/or maintenance of diffuse noxious inhibitory pain control (DNIC) produced by peripheral tactile stimulation and/or environmental or behavior-
al stimuli (44).

Dorsal Column Pain Modulation

A-beta driven, low threshold mecha-
nosensitive WDR cells can modulate no-
ciceptive activity of the STT. Low inten-
sity mechanical stimuli activate interneu-
rons in laminae II, IIa, and IV that link the 
fibers of WDR cells of the non-nocicep-
tive dorsal columns with fibers of the STT and produce inhibitory post-synaptic po-
tentials (IPSPs) in STT cells. These IPSPs have a longer duration than the initiating low intensity stimulus, and cause brief, but summative, inhibition of nocispon-
sive WDR and NS cells of the STT. The 
dorsal column projects to the medullary nuclei cuneatus and gracilis, decussates at 
this level, and ascends as the medial lem-
niscal pathway to project to the VPL, ven-
tromedial, and pulvinar thalamic regions. Low level phasic or high frequency repet-
titive stimulation of medial lemniscal-tha-
lamic pathways can suppress volleys of nociceptive STT inputs, preventing noc-
iceptive thalamic activity and thalamo-
cortical transmission (45).

There is evidence that A-beta mechanoreceptor/dorsal column stimu-
lation may engage central oxytocin-me-
diated mechanisms to enhance corti-
co-limbic and midbrain-centrifugal sys-
tems that mediate sensory and perhaps aversive cognitive dimensions of pain, ei-
ther specifically or as part of DNIC (46). These substrates are partly responsible for the clinical analgesic effects of dorsal col-
umn electrostimulation (DCS) and possi-
bly certain manual and tactile therapeutic approaches. Such effects, however, appear to be of relatively short duration and may become ineffective against progressive, in-
creasing pain.

Continuous A-delta and C-fiber ac-
tivity can functionally and microstruc-
turally remodel the STT and supraspinal nociceptive pathways to potentiate pain transmission, thereby overcoming spinal or thalamic suppression by dorsal column input. Also, C-fiber-mediated neurogen-
ic inflammation induces production of nerve growth factor (NGF) that is released into both peripheral tissue and within the dorsal root ganglia. NGF alters transcription 
processes in A-beta fibers, causing 
them to express vanilloid receptors, TTX-
sensitive and TTX-resistant Na+ channels, 
Na+-sensitive voltage-gated Ca2+ can-
nels, and produce the peptides sub-P and 
CGRP, characteristics associated with no-
ciceptive afferent fibers. NGF-exposed A-
beta fibers also exhibit synaptic rearrange-
ment, extending collaterals into lamina II and IIa to synapse upon NS and WDR 
cells (47). Altered physiologic responses to 
mechanical input and the synaptic con-
nectivities in laminae II and IIa can in-
duce transmission of non-noxious stimuli 
that are interpreted as painful. This mech-
anism is responsible both for the loss of 
dorsal column-mediated pain control and for a component of mechanical alldyn-
ia that follows neurogenic inflammation and peripheral neuropathic insult.

Hormonally-Mediated Pain Modulation

Several hormonal systems have been 
shown to modulate pain. The hypothe-
lamic-pituitary-adrenal (HPA) axis is of 
particular note in that both hypothalam-
ic corticotropin releasing factor (CRF) 
and pituitary adrenocorticotropic hor-
mon (ACTH) produce moderate anal-
gesia. This effect is partially opioid-de-
pendent, suggesting that the corticotro-
pins may both mediate the stress response and induce the synthesis and release of the parent molecule, pro-opiomelanocortin (POMC), leading to facilitated produc-
tion of ACTH and opioids to further en-
hance responsibility to stress and pain (48).

Pain-induced release of opioids from the 
PAG and NE from the RMC act at the hy-
Fig. 4. Pathways of bulbospinal and centrifugal analgesia. Afferent input from the STT activate brainstem 5-HT and/or NE systems to release monoamines within the dorsal horn. 5-HT post-synaptically inhibits nociceptive afferents and may engage inhibitory interneurons within the dorsal horn to indirectly reduce output of nociceptive afferents. Norepinephrine directly inhibits firing of nociceptive afferents. Opioids released from the PAG can disinhibit descending 5-HT and NE systems to evoke mesencephalic centrifugal analgesia. Opioids released from the PAG/PVG can also act at spinal opioid receptors to produce pain modulation. The limbic forebrain can activate the PAG to induce descending, centrifugal, bulbospinal and diffuse pain control. A description of these systems is afforded in the text.
Table 4. Physiologic and pharmacologic properties of spinal and supraspinal pain modulating systems

<table>
<thead>
<tr>
<th>SYSTEM &amp; ANATOMY</th>
<th>CHEMISTRY &amp; PHYSIOLOGY</th>
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<tbody>
<tr>
<td><strong>INTRASPINAL</strong></td>
<td></td>
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<tr>
<td><strong>SEGMENTAL INTERNEURONS</strong></td>
<td></td>
</tr>
</tbody>
</table>
| Interneurons in laminae II, V | Opioid: Dynorphin: Acts at K+, OR, receptors  
G-protein mediated  
K+, Ca++ mediated hyperpolarization  
Leu/mentenkephalin: Acts upon OR, and OR, receptors  
G-protein mediated  
K+ mediated hyperpolarization  
GABA: Acts upon GABA, receptors  
G-protein mediated  
Cl- mediated hyperpolarization  
Glycine: Acts at glycine receptors  
Cl- mediated hyperpolarization  
Anandamide: Acts at CB1 receptors  
Membrane stabilization/hyperpolarization |
| Synaptic contact with recurrent processes of A-delta fibers | 5-HT: Acts upon post-synaptic 5-HT, receptors on (pre-synaptic) primary afferents  
and (post-synaptic) second-order neurons  
G-protein mediated inhibition of cation current(s)  
Hyperpolarizing; inhibitory  
NE: Acts upon post-synaptic alpha, receptors on (pre-synaptic) afferents and second-order afferents  
G-protein mediated inhibition of cation current(s)  
Graded hyperpolarization, inhibitory |
| **BULBOSPINAL** |                        |
| **NRM** | Opioid: Leu/mentenkephalin: Acts at OR, and OR, receptors  
G-protein mediated K+ hyperpolarization  
endorphin: Acts at OR receptors  
G-protein mediated K+ hyperpolarization  
orphanin: Acts at OR, receptor  
K+ efflux, inhibition of voltage-gated Ca++ channels |
| Fibers from NRM descend via DLF  
Mono- and polysynaptic contacts with primary and second-order units of dorsal horn  
Synapse upon interneurons  
5-HT: Acts upon post-synaptic 5-HT, receptors on primary afferents and second-order neurons  
G-protein mediated inhibition of cation current(s)  
Hyperpolarizing; inhibitory  
NE: Acts upon post-synaptic alpha, receptors on (pre-synaptic) afferents and second-order afferents  
G-protein mediated inhibition of cation current(s)  
Graded hyperpolarization, inhibitory |
| **RMC** |                        |
| Fibers from NRcG/NRpG descend via DLF  
Mono- and polysynaptic contacts with primary and second-order afferents of dorsal horn  
5-HT: Acts upon post-synaptic 5-HT, receptors on primary afferents and second-order neurons  
G-protein mediated inhibition of cation current(s)  
Hyperpolarizing; inhibitory  
NE: Acts upon post-synaptic alpha, receptors on (pre-synaptic) afferents and second-order afferents  
G-protein mediated inhibition of cation current(s)  
Graded hyperpolarization, inhibitory |
| **MIDBRAIN** |                        |
| **PAG** | Opioid: Leu/mentenkephalin: Acts at OR, and OR, receptors  
G-protein mediated K+ hyperpolarization  
endorphin: Acts at OR receptors  
G-protein mediated K+ hyperpolarization  
orphanin: Acts at OR, receptor  
K+ efflux, inhibition of voltage-gated Ca++ channels |
| PVG | 5-HT: Acts upon post-synaptic 5-HT, receptors on primary afferents and second-order neurons  
G-protein mediated inhibition of cation current(s)  
Hyperpolarizing; inhibitory  
NE: Acts upon post-synaptic alpha, receptors on (pre-synaptic) afferents and second-order afferents  
G-protein mediated inhibition of cation current(s)  
Graded hyperpolarization, inhibitory |

Pothalum to produce increased levels of induced nitric oxide (iNO). iNO produces vasodilatation within the pothalamic median eminence, increasing CRF and stimulating phasic release of ACTH from the anterior pituitary. Changing levels of ACTH can affect adrenally-mediated stress responses and regulate the production of POMC-derived opioid peptides that have pain- and immuno-modulatory activity (48). Acute and durable pain can engage spinal sympathetic innervation and act through the reticular-parabrachial-hypothalamic pathway to induce autonomic responses. Sympathetic stimulation of the chromaffin cells of the adrenal medulla causes the release of adrenal opioids enkephalin and endorphin, plus epinephrine, into the systemic circulation. Adrenal opioids act at mu/OR3 and delta/or1 opioid receptors of the peripheral nervous system to produce analgesia; changes in immune and metabolic function are mediated by...
the actions of these ligands at mu, opioid and heterogeneous adrenergic receptors in non-neural tissues such as immunocytes, mast cells, vascular and enteric smooth myocytes, and adipocytes (49, 50).

CONCLUSION

Advances in pain medicine reflect rapid progress in basic, clinical, and more recently, the philosophical domains of research. Systems-mediating nociception and anti-nociception are diverse, and research has just begun to elucidate the implications of such diversity. The theoretical dialectic surrounding conceptualization of peripheral versus central neural sensitization has been reconciled by recognition of nociceptive facilitatory mechanisms that exist throughout the nervous system. Recognition of heterogeneous chemical and molecular mediators of nociception and anti-nociception has fostered revised insight into the complexity of these substrates, and to a realization of the multitude of physiologic effects produced by and subserving pain. By understanding the anatomy, physiology, and neurochemistry of these systems, we may come to appreciate pain both as a neurologic disease process and as an illness phenomenon of the mind, an understanding that will aid in developing more effective research strategies and clinical approaches to expand therapeutic effectiveness against specific types of pain.

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