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Pain pathways and mechanisms of neuropathic pain

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NEURAL PROCESSING OF PAIN SIGNALS

Several neural steps are involved in the processing of noxious signals that can lead to the experience of pain.

- Transduction is the process by which noxious stimuli are converted to electrical signals in the nociceptors. Unlike other sensory receptors, nociceptors are not specialized from a structural point of view, but rather exist as free nerve endings. Nociceptors readily respond to different noxious modalities such as thermal, mechanical or chemical stimuli, but ***nociceptors do not respond to non-noxious stimuli***. Also in contrast to other types of sensory receptors, ***nociceptors do not adapt***–that is, continued stimulation results in continuous or repetitive firing of the nociceptor and, in some cases, continued stimulation actually results in a decrease in the threshold at which the nociceptors respond (ie, sensitization of nociceptors. Neurotransmitters that are produced within the cell body–ie, in the dorsal root ganglia (DRG) are the same at both the central and peripheral ends of the nerve fiber and are released at both ends, participating in producing the pain signal centrally, as well as in promoting events that lead to additional pain peripherally. The release of neurotransmitters from the peripheral terminals of the afferent fibers is actually an "efferent" function of these afferent neurons. Peripheral release of neurotransmitter substances lead to the classic "axon reflex", a reflex that does not require the spinal cord–this reflex leads to peripheral changes that are well recognized to contribute to pain.
- ***Transmission*** is the second stage of processing of noxious signals, in which information from the periphery is relayed to the thalamus and then to the cortex. Noxious information is relayed mainly via 2 different types of primary afferent nociceptive neurons, which conduct at different velocities.

A-delta fibers are thinly myelinated fibers which conduct in the range of 2 m/s to 20 m/s. All fibers respond to high intensity mechanical stimulation and are therefore termed ***high threshold mechanoreceptors***. Some, but not all fibers also respond to thermal stimuli–the latter are termed mechano–thermal receptors.

C-fibers are non-myelinated fibers that conduct in the range of 0.5 m/s to 2 m/s and transmit noxious information from a variety of modalities including mechanical, thermal, and chemical stimuli–for this reason, they are termed ***C-polymodal nociceptors***.

As the nociceptive afferent fibers approach the spinal cord, the "dorsal root entry zone", axons of different sizes begin to segregate so that the large myelinated Aβ fibers (carrying non-nociceptive information such as proprioception, light touch, etc.) separate from the small thinly myelinated and nonmyelinated C fibers; the nociceptive fibers (and C) separate into the ventral portion of the nerve. By the time the root actually penetrates the spinal cord, the larger diameter non-nociceptive fibers continue medially to form the dorsal columns and generally do not participate in pain transmission. These large myelinated fibers also send collateral projections into the deeper aspects of the dorsal horn of the spinal cord. The and C nociceptive fibers branch into a fiber tract called "Lissauer's tract" and travel rostrally or caudally in this tract for a few segments (up to 4) before entering the dorsal horn of the spinal cord. Primary afferent fibers then synapse on a "second-order" pain transmission cell. This is the cell which will send its process across the midline into the anterolateral aspect of the spinal cord white matter, join with many other similar fibers and form the ascending "spinothalamic tract" that leads to the thalamus. It is in the thalamus that the second-order cell synapses with the third-order cell that projects to the cortex.

In addition to the synapse of the primary afferent neuron in the spinal dorsal horn with the second-order cell (also called the projection neurons) just described, the af-

ferents also synapse with excitatory interneurons and inhibitory interneurons. Projection neurons in the dorsal horn are those that "project" to higher levels of the nervous system. Projection neurons that respond specifically to nociceptive stimuli are called "nociceptive specific" (NS) cells, while other projection neurons that respond to both noxious and to innocuous stimuli are called "wide dynamic range" (WDR) neurons. The WDR neurons are localized deeper in the dorsal horn of the spinal cord and respond to afferent input from many different fibers in the periphery and so have large "receptive fields". WDR neurons receive inputs, for example, from the large myelinated fibers that mainly function to transmit light touch and proprioception in the dorsal white columns–remember, these fibers send collateral projections into the deeper aspects of the spinal dorsal horn where they synapse with the WDR neurons. The NS neurons are localized more superficially in the spinal dorsal horn and have a restricted range of input from peripheral sites (ie, a small receptive field). The second–order cells in the spinal dorsal horn also have the capacity to change their response patterns in the circumstance of sustained discharge of afferent fibers (as would occur in the setting of an injury). Under these circumstances, these cells respond at lower thresholds and from inputs over a broader area in the periphery (ie, have expanded "receptive fields")–in other words, the secondorder cells become "sensitized". This is termed "central sensitization" and also contributes to the phenomena of hyperalgesia and allodynia.

The gray matter of the dorsal horn of the spinal cord is organized into sheets that are elongated in the rostrocaudal axis. This type of organization has served as the basis of dividing the dorsal horn gray matter into 6 different "lamina" (numbered in a dorsal to ventral scheme–10 lamina are recognized in the dorsal and ventral horn).

These lamina have been classified on the basis of the appearance of neurons, their size, orientation, and density.

The nociceptive afferent fibers synapse in several layers, but especially in lamina I (the marginal zone) and lamina II (the Substantia gelatinosa) Collectively, lamina I and II are called the superficial layer of the dorsal horn of the spinal cord). The nociceptive afferent fibers also synapse in lamina V and other deeper layers. The site of termination of these nociceptive afferents is important in that these areas of the spinal cord are those that are most important in the rostral transmission of the pain signal. The NS cells are found in the superficial lamina of the spinal dorsal horn, while the WDR neurons are localized in deeper lamina (ie, lamina V) of the spinal dorsal horn.

Once the nociceptive afferents have terminated in the dorsal horn of the spinal cord, they transmit the signal from the periphery by releasing specific neurotransmitters that are associated with pain. While we cannot say with complete certainty which neurotransmitters are the "pain transmitters" we can identify some important and likely candidates. These candidate neurotransmitters must be identified within the cell body (in the DRG) of the nociceptive afferent neuron. One of the most important candidates is a small amino acid called glutamate that can interact with both NMDA-type and non-NMDA excitatory amino acid receptors. Another important transmitter that is probably associated with the transmission of pain is an 11 amino acid peptide called "substance P". This peptide is released both centrally and peripherally following stimulation of the nociceptive afferent fiber. Furthermore, local application of substance P within the spinal cord results in a depolarization of postsynaptic neurons in the dorsal horn of the spinal cord, similar to that seen with electrical stimulation of the nociceptive afferent fiber. Substance P interacts with tachykinin receptors and serves to initiate depolarization of the

Opioids: Positive controlled trials

Study	Agent (mg/d)	N	Weeks	Primary end point
Pianful DPN				
Gimbel	CR oxycodone (20-120, PBO)	159	6	Pain intensity
Harati	Tramadol (50-400, PBO)	131	6	Pain intensity
Watson	CR oxycodone (20-80, PBO)	45	8	Mean daily pain
PHN				
Raja	CR morphine (15-240, PBO)	76	24	Pain intensity, relief; cognitive function
Watson	CR oxycodone (20-60, PBO)	50	8	Pain intensity, relief

PBO = placebo

Gimbel et al. *Neurology*. 2003; 60: 927-934, Harati et al. *Neurology*. 1998; 50: 1842-1846. Watson et al. *Pain*. 2003; 105: 71-78. Raja et al. *Neurology* 2002; 59: 1015-1021. Watson, Babul, *Neurology* 1998; 50: 1837-1841.

Tricyclic antidepressants: Positive controlled trials

Study	Agent (mg/d)	N	Weeks	Primary end point
Painful DPN				
Max	Amitriptyline (25-150, PBO)	29	12	Pain relief
Max	Desipramine (12.5-150, PBO) Amitriptyline (12.5-150, PBO)	108	14	Pain relief
Sindrup	Desipramine, (50 or 200, PBO), Clomipramine (50 or 75, PBO)	26	6	Neuropathy Symptoms
Max	Desipremine (12.5-250, PBO)	20	12	Pain relief
PHN				
Watson	Amitriptyline (≥ 12.5, PBO)	24	8	Pain relief
Max	Amitriptyline (12.5-150, PBO)	58	12	Pain relief
Graff-Radford	Amitriptyline (12.5-200, PBO)	49	8	Pain intensity
Kishore-Kumar	Desipramine (12.5-250, PBO)	26	12	Pain relief
Raja	Nortriptyline (10-160, PBO)	76	24	Pain intensity, relief, cognitive function

Max et al. *Neurology* 1987;37:589-596; Max et al. *N Engl J Med* 1992;326:1250-1256; Sindrup et al. *Br J Clin Pharmacol* 1990;30:683-691; Max et al. *Pain* 1991;45:3-9; Watson et al. *Neurology* 1982;32:671-673; Max et al. *Neurology* 1988;38:1427-1432; Graff-Radford et al. *Clin J Pain* 2000;16:188-192; Kishore-Kumar et al. *Clin Pharmacol Ther* 1990;47:305-312; Raja et al. *Neurology* 2002;59:1015-1021.

Tricyclic antidepressants

Drug	Sedation	Ach effect	Orthostatism	Cardiac
Amitriptyline	+++	++++	+++	+++
Nortriptyline	+++	+	+	++
Desipramine	+	+	++	++
Doxepin	+++	++	++	++

Alvarez W, et al. Pharmacotherapy 2003;23:754

SNRIs: Positive controlled trials

Study	Agent (mg/d)	N	Weeks	Primary end point
Painful DPN				
Rowbotham	Venlafaxine (75 or 150-225, PBO)	244	6	Mean change in VAS-PI, VAS-PR
Duloxetine study 1	Duloxetine (20, 60, or 120; PBO)	457	12	End point mean pain score
Duloxetine study 2	Duloxetine (60 or 120, PBO)	334	12	End point mean pain score

PBO = Placebo; VAS-PI = Visual Analog Scale of Pain intensity; VAS-PR = Visual Analog Scale or Pain Relief; SNRI = serotonin-norepinephrine reuplake inhibitor.
Goldstein DL, et al. *Pain* 2005;116:109-118; Rowbotham et al. *Pain* 2004; 110:697-706; Physicians' Desk Reference® 59th ed. 2005

second order neuron. This change in membrane potential is important in that "voltage-dependent" channels begin to open, including the NMDA channel that is activated by glutamate. So, both of these neurotransmitters will interact with receptors on the postsynaptic membrane, and depend on the activity of the other transmitter, to initiate the process of transmission of the pain signal. Knowledge of these transmitters is crucial in understanding mechanisms by which pain-relieving drugs, such as morphine, can produce their effects.

Once the signal has been transmitted to the second-order neurons, these cells send their projections across the mid-

Anticonvulsants: Positive controlled trials

Study	Agent (mg/d)	N	Weeks	Primary end point
Painful DPN				
Wilton	Carbamazepine (600, PBO)	40	4	Pain relief
Rull	Carbamazepine (600, PBO)	30	6	Neuropathy symptoms
Backonja	Gabapentin (900-3,600, PBO)	165	8	Daily Pain severity
Eisenberg	Lamotrigine (25-400, PBO)	59	6	Pain intensity
PHN				
Rice	Gabapentin (1,800 or 2,400, PBO)	334	7	Mean daily pain
Rowbotham	Gabapentin (300-3,600, PBO)	229	8	Mean daily pain

Wilton. *S Afr Med J* 1974;48:869-872; Rull et al. *Diabetologia* 1969;5:215-218; Backonja et al. *JAMA* 1998;280:1831-1838; Eisenberg et al. *Neurology* 2001;57:505-509; Rice, Maton. *Pain* 2001;94:215-224; Rowbotham et al. *JAMA* 1998;280:1837-1842.

Neuropathic pain

Drug	Starting dose	Target dose	Side effects*	Renal Exc	Hepatic pathways
Neurontin	100-300	3,600	Weight gain, twitching, HA > 95%	No	
Trileptal	300	2,400	Hypo Na^{++}, SJS, and EM	30%	Yes, ~ 50%
Zonegran	100	600	Weight loss, renal stones	35%	Yes, ~ 50%
Topamax	25-50	400	Weight loss, renal stones	60-70%	Yes, ~ 30%?
Pregabalin	50-75	300	Weight gain, visual changes	> 90%	No

* dizziness, sedation, ataxia, blurred vision, and diplopia

line and ascend to the thalamus via the ***anterolateral system***. The anterolateral system consists mainly of the "spinothalamic tract", which has been broken down in general terms into the neospinothalamic and the paleospinothalamic (ie, spinoreticulothalamic) tracts. The spinothalamic tract is the "freeway" to the thalamus, while the spinoreticulothalamic tract sends its signals along the "local streets".

The location of the spinal pathway for rostral transmission is therefore in the anterolateral quadrant of the spinal cord. Surgical lesions of the anterolateral spinal cord have been used to control pain in some cases. Most patients who have an anterolateral cordotomy experience a profound loss of pain (and temperature) sensation on the side opposite the lesion. The upper limit of the loss of sensation is about 4 segments below the level of the lesion (remember that afferent fibers travel for a few segments rostrally in Lissauer's tract prior to synapsing in the dorsal horn). It is important to note that the effects of cordotomy are variable, incomplete and in many cases, transient. Sensitivity, or partial sensitivity, may be retained in some portions of the periphery. The reasons for the transient nature, in some cases, of cordotomy are unclear, but indicate that there may be several routes by which the nociceptive message can reach higher centers.

Spinothalamic tract neurons terminate in specific nuclei of the thalamus, each of which projects to different cortical areas. In general, neospinothalamic tract neurons project to the lateral thalamus and this pathway projects further, through the third-order neuron, to the somatosensory cortex, while the paleospinothalamic tract pathway projects to the medial thalamus and to the association cortex. This emphasizes that there are parallel pathways to the cortex and each of these may make a contribution to the complex human perception of pain.

- ***Modulation*** is a third and critically important aspect of the processing of noxious stimuli that occurs–this process represents the changes which occur in the nervous system in response to a noxious stimulus and allows the noxious signal received at the dorsal horn of the spinal cord to be selectively ***inhibited,*** so that the transmission of the signal to higher centers is modified. There is an endogenous pain modulation system, consisting of well-defined ***descending neural tracts*** that can inhibit rostral transmission of the pain signal.

Activation of this system is thought to involve the release at supraspinal locations of neurotransmitters, including beta-endorphin (eg, ß-endorphin) and enkephalins.

These peptides represent 2 families of endogenous peptides that are believed to produce pain relief, mainly under situations of stress. This is critically important to you as a physician because when you relieve your patients' pain with narcotics, you give drugs that mimic the actions of these endogenous neurotransmitters. Morphine, probably the most clinically important pain-relieving drug, is derived from the poppy plant, but acts by binding to the same opioid receptors that bind the endogenous opioids–for this reason, the endogenous opioids are called "endorphins" or "endogenous morphine". Remember, of course, that it is morphine that mimics the action of the endorphins, since these are the physiological transmitters involved in the modulatory process.

Descending modulatory systems: Activation of the descending system by the endorphins occurs through specific receptors called "opioid receptors". These systems are activated in and around the periaqueductal gray (PAG) region of the midbrain, and such neurons then project to sites in the medulla (eg, nucleus reticularis gigantocellularis, nucleus raphe magnus) and the locus coeruleus (the major source of norepinephrine cells in the brain) through uncertain circuitry where other neurons are activated (probably through disinhibition–that is, inhibition of a tonically active inhibitory interneuron). These descending fibers then project to the dorsal horn of the spinal cord along a tract called the dorsolateral funiculus (located in the dorsolateral portion of the spinal cord) to synapse with either the incoming primary afferent neuron, the second-order pain transmission neuron, or interneurons. Again, the circuitry that occurs at the spinal level is uncertain. In general, however, these descending pain modulatory neurons[(1)] release nonopioid neurotransmitters in the spinal cord, especially serotonin (5HT) and norepinephrine (NE) or[(2)] activate small opioid containing interneurons in the spinal dorsal horn to release opioid peptides (again through disinhibition). The released NE and 5HT (acting through some types of 5HT receptors) can act to[(1)] directly inhibit the release of transmitters from the incoming nociceptive afferent signal, and[(2)] to inhibit the second–order pain transmission cell. Both of these will produce an inhibition of transmission of the pain signal. As mentioned above, NE and 5HT released from these descending pathways can also activate (indirectly) the release of endogenous opioids from interneurons, again through aprocess of disinhibition. Activation of the descending pain modulatory system is a good example of why subjects report not feeling pain at all under conditions of stress, or perhaps other situations, where even though thepain is felt, the degree appears to be greatly modulated.

Sites of action of endogenous and exogenous opioids: The small local interneurons in the spinal dorsal horn containing endogenous opioid transmitters deserve special emphasis. These small inhibitory interneurons can release opioid peptides that act on opioid receptors located on[(1)] the central terminals of the primary afferent C fibers to directly inhibit the incoming pain signal and[(2)] on cell bodies of the second-order transmission neurons, to inhibit the transmission of the pain signal to higher centers. Opioid receptors are also localized on the peripheral terminals of the nociceptive C fibers–the latter provides an additional target for opioids in the management of pain. The actions of exogenous opioids (ie, administered by you) will mimic the site of action of endogenous opioids. Systemically administered opioid (eg, morphine) will distribute to the spinal cord where it will act to block inputs from C-fibers and to the periphery where it will block activation of C-fibers. Second-order pain transmission cells will also be blocked by spinally administered opioids. Finally, systemically given opioids will distribute to brainstem sites such as the PAG to activate the descending pain modulatory system. The descending system (described above) and the local system in the spinal dorsal horn and in the periphery are all active at the same time.

Summary of sites of opioid action: we can identify 4 sites where opioids can act to relieve pain. When you give morphine, or other opiates, to patients you are[(1)] activating the opioid receptors in the midbrain and "turning on" the descending systems (through disinhibition)[(2)], activating opioid receptors on the second-order pain transmission cells to prevent the ascending transmission of the pain signal[(3)], activating opioid receptors at the central terminals of C-fibers in the spinal cord, and[(4)] activating opioid receptors at the peripheral terminals of the nociceptive C-fibers. It is the activation of these 4 systems that allows opiates such as morphine to produce clinically useful pain relief. Endogenous opioid released from opioid-expressing cells clearly act at sites 1, 2, 3, and possibly 4 (through invasion of injury sites by opioid receptor expressing immune cells).

- Perception is the final part of the process where there is subjective interpretation by the cortex of the stimulus as pain. This process can be artificially described as involving 2 types of cortical processing. The ***sensory component*** of cortical processing is that in which the stimulus can be classified as noxious, its stimulus intensity decoded, and its location identified. However, before such signals represent the true "experience of pain", something that is only a human experience, the cortex overlays an additional aspect to the neural processing, described as the ***affective component*** of pain. Here, the cortex relates the situation and the history of such noxious stimuli to the interpretation of the strict sensory component. Again, the importance of the noxious stimulus in contributing to the experience of pain is "interpreted" in light of the situation and is much worse in pathological states, such as those associ-

ated with disease where the patient sees the pain as a signal of progression of the disease. This is one of the reasons why it is so difficult to measure pain in humans.

Therapy with tricyclic antidepressants and anticonvulsants will complete the therapeutic protocol for the treatment of neuropathic pain. The side effect profile dictates the choice of medication in the case of tricyclic antidepressants, and to certain extent the use of anticonvulsants as well. The following tables outline silent issues regarding these medications:

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