Neurobiology of Pain

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Pain

• Definition
  – An unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage

*International Association for the Study of Pain*
• Pain protects humans by warning of occurrence of biologically harmful processes
  – people protect themselves from burns, bruises and wounds
    • primarily due to reflex activity
    • but also because of associated emotional arousal
  – reflexes, regulated at the level of spinal cord, protect by removing a body part away from danger
  – associated emotional arousal, experienced as distress or fear, may also motivate a person to move away from a painful stimulus
  – Fear of pain can also prevent a person from moving, which in turn promotes healing of the injury resulting in that pain
  – pain may elicit an empathic, comforting, and health promoting behavior in people observing a person in pain.
Interfering nature of Pain

- Pain can interfere with daily functioning of a person when it prevents people from performing their
  - social roles,
  - vocational roles, and
  - impacts their psychological well-being.

- To appreciate this duality of pain, i.e. protective and interfering nature of pain, one must understand the CNS mechanisms of pain transmission and regulation.

http://www.surfaidinternational.org/site/apps/nl/content2.asp?c=ekLPK4MOIsG&b=354323&ct=412953
Types of Somatic Sensations

Skin

- Pain
- Temperature
- Touch
  - Pressure
  - Vibration

Musculoskeletal System

- Proprioception
  - Position Sense
  - Kinesthesia
- Pain
Transmission/Perception of Pain

- Four specific parts of the nervous system transmit pain signals from the periphery to the higher centers of the CNS:
  - the nociceptors,
  - the dorsal horn neurons,
  - the ascending tracts, and
  - the supraspinal projections.

Robinson(1997), Journal of Hand Therapy
Nociceptors

- Nociceptors, one type of somatosensory receptors, are the first order neurons of pain pathways.
  - Free nerve endings

- These receptors generate pain signals in response to harmful stimuli.

- Different types of nociceptors have been identified that respond to
  - mechanical,
  - heat and
  - chemical stimuli, or
  - any combination of these stimuli.
• Cell bodies of the nociceptors reside in the dorsal root ganglia (DRG).
• Nerve fibers leaving the DRG bifurcate and send one branch to the periphery and the other branch to the dorsal horn (DH).
• The peripheral fibers conduct pain signals from the skin, muscles, fascia, vessels, and joint capsules to the DRG.
Peripheral fibers transmitting pain and other somatosensations, and therefore called the sensory peripheral fibers, have been classified into three types based on their diameter, myelination and conduction velocity: the A (with four subtypes – α, β, γ and δ), B and C-fibers.

- The A-δ fibers and C-fibers conduct pain signals, but, at different velocities.
- A-δ fibers (Myelinated) conduct fast pain (a sensation experienced immediately after an injury that indicates location of injury).
- C-fibers (Unmyelinated) conduct slow pain (follows sharp pain and can be characterized as a dull, throbbing ache with poor localization).

<table>
<thead>
<tr>
<th>Group</th>
<th>Myelination</th>
<th>Diameter (μm)</th>
<th>Velocity (m/s)</th>
<th>Mediates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aα</td>
<td>Yes</td>
<td>1–20</td>
<td>5–120</td>
<td>Touch, proprioception cold, vibration, sharp pain, kinesthesia</td>
</tr>
<tr>
<td>B</td>
<td>Yes</td>
<td>1–3</td>
<td>3–15</td>
<td>Visceral sensation</td>
</tr>
<tr>
<td>C</td>
<td>No</td>
<td>0.2–5</td>
<td>0.5–2.3</td>
<td>Aching pain, cold, warmth</td>
</tr>
</tbody>
</table>

This group is subdivided into Aα (proprioception), Aβ (touch, proprioception) and Aδ (sharp pain, cold).

Investigators differ in their report of diameters.
Second Order Neurons

- Two types of second order neurons perceive pain:
  - nociceptive specific (NS) neurons and
  - wide dynamic range (WDR) neurons.
- The NS and WDR neurons conduct pain signals to the brain via various ascending tracts in the spinal cord.
- NS respond to noxious stimuli
- WDR respond to both innocuous and noxious stimuli.
- Axons of the second order neurons (the NS and WDR neurons) form the ascending tracts, through which pain signals travel in the spinal cord.

Robinson (1997), Journal of Hand Therapy
Table 1: Differences between nociceptive specific (NS) and wide dynamic range (WDR) neurons based on Covington (2000) and Robinson (1997)

<table>
<thead>
<tr>
<th>Difference</th>
<th>Nociceptive Specific (NS) Neurons</th>
<th>Wide Dynamic Range (WDR) Neurons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Activating fibers</td>
<td>A-δ and C fibers</td>
<td>A-β, A-δ and C fibers</td>
</tr>
<tr>
<td>Activating stimuli</td>
<td>Nociceptive (fast and slow pain)</td>
<td>Innocuous (cutaneous touch and pressure) and Nociceptive (fast and slow pain)</td>
</tr>
<tr>
<td>Location</td>
<td>Mostly in Lamina I of spinal cord</td>
<td>Mostly in Lamina IV and V of spinal cord</td>
</tr>
<tr>
<td>Lamina I</td>
<td>Somatotopically organized</td>
<td>Not present, not somatotopically organized</td>
</tr>
<tr>
<td>Pain receptive field</td>
<td>Restricted to relatively small areas</td>
<td>Vary with stimulus strength; much larger than those of NS neurons</td>
</tr>
<tr>
<td>Discharge strength</td>
<td>Vigorous increase in discharge as a result of noxious stimuli (e.g. pinching and strong compression)</td>
<td>Discharge at lower levels in response to innocuous stimuli; discharge more vigorously in response to noxious stimuli</td>
</tr>
<tr>
<td>Contribution to Spinothalamic Tract</td>
<td>Make up 20 – 25% of tract</td>
<td>Make up about 75% of tract</td>
</tr>
<tr>
<td>Function</td>
<td>Involved in sensory-discriminative aspects of pain (localization of pain; nature of stimulus)</td>
<td>Involved in affective-motivational aspects of pain (intensity; differences in noxious stimuli; initiation of complex behavioral responses to pain)</td>
</tr>
<tr>
<td>Pain theory supported</td>
<td>Specificity theory: presence of specific neurons activated only by noxious stimuli</td>
<td>Pattern theory: presence of second order neurons that discharge differently to noxious and innocuous stimuli</td>
</tr>
</tbody>
</table>
Ascending Tracts: Fast Pain

• Different ascending tracts conduct fast and slow pain signals.

• Fast pain travels via the neospinothalamic tracts. The fast pain transmitting A-δ fibers predominantly terminate on the nociceptive specific (NS) neurons.

• The axons of the NS neurons cross the midline of spinal cord in the anterior white commissure.

• The crossed NS axons ascend to the thalamus as the lateral spinothalamic tract.

• Also called the lateral pain pathways

Shechtman, Course manual for Nervous System and Disorders
Postcentral gyrus

Ascending pathways

Thalamus

Spinal cord

Messages passed from the thalamus to the cerebral cortex

Messages passed up the spinothalamic pathway to the thalamus

A-delta
Ascending Tracts: Slow Pain

- Slow pain travels via multiple parallel ascending pathways.
- The slow pain transmitting C-fibers terminate on interneurons in the DH.
- The interneurons synapse with WDR neurons in the DH.
- The WDR axons ascend to the midbrain as spinomesencephalic tract, reticular formation as spinoreticular tract, and thalamus as paleospinothalamic tract.
- Slow pain signals primarily ascend via the paleospinothalamic tract. The other two tracts serve functions of arousal, motivation, reflexive function, and activation of descending fibers.
- Also called medial pain pathways
Thalamus contains nerve centers responsible for vision, hearing reflexes, equilibrium and posture. **It also relays pain signals to the cerebrum.** Crude sensation reaches consciousness in the thalamus, the cerebral cortex is responsible for the higher thought processes such as emotion and interpretation.
Supraspinal Projections: Fast Pain

- The NS axons, that conduct fast pain, mostly end in the ventral posterolateral (VPL) nucleus of the thalamus.
- Third order neurons arise from the VPL nucleus and project to the primary somatosensory cortex (SI) and the secondary somatosensory cortex (SII).
- These projections allow for interpreting sensory features of pain, which includes location, intensity and quality of pain.
Supraspinal Projections: Slow Pain

- Axons from the retina (i.e. optic nerve) form 3 pathways: 1) Optic nerve to optic chiasm, to optic tract ending in lateral geniculate body/nucleus.
- From LGB, these fibers go to the visual cortex in the optic lobe.
- This pathway is responsible for visual identification and visual guidance.

http://universe-review.ca/I10-80-midbrain.jpg
Supraspinal Projections: Slow Pain

- 2) Fibers from the retina end in the pretectal area for controlling pupillary reflexes.
- 3) Fibers from the retina also end in the superior colliculus of the Tectum.
- These fibers role is orientation and visually guided movements of the eyes.

http://universe-review.ca/I10-80-midbrain.jpg
Supraspinal Projections: Slow Pain

- The tracts conducting slow pain (the spinomesencephalic, spinoreticular, and paleospinothalamic tracts) terminate in different areas of the brain.
- The spinomesencephalic tracts conduct pain signals to the superior colliculus and periaqueductal gray and finally to the hypothalamus and raphe nuclei.
  - These areas assist in turning the eyes and head towards the noxious stimulus.
The spinoreticular tracts terminate in the reticular formation in the brainstem. The paleospinothalamic tracts project to the midline and intralaminar nuclei of the thalamus. These nuclei further project to basal ganglia (BG), prefrontal cortex (PF), anterior cingulate cortex (ACC), and primary motor cortex (M1).

Together, activity in the spinoreticular and paleospinothalamic tracts results in arousal, withdrawal, and autonomic and affective responses to pain.

The Matrix and Circuitry of Pain

- Based on PET imaging studies, the areas most often cited as being a part of a pain matrix include the anterior cingulate, insular, prefrontal, inferior parietal, primary and secondary somatosensory (SI and SII), and primary motor and premotor cortices.

- In addition, the thalamus, brain stem, and cerebellum (which is not typically thought of as being a pain center) frequently are included in this complex, based on experiments involving painful stimulation.
Under physiologic conditions, pain sensations are mediated by high-threshold, fine myelinated (Aδ) and unmyelinated (C) afferent neurons (i.e., nociceptors). Tissue injuries release chemicals that trigger the transmission of pain signals along the nociceptors, which form synapses with neurons in the dorsal horn of the spinal cord. From the dorsal horn, the signal is transmitted along the spinothalamic tract to the cerebral cortex. The ascending component transmits pain information to the brain from the periphery through the spinal cord, thalamus, pain information is transmitted collaterals to the mid-brain and other structures. To complete the circuit, there are important descending pathways that modulate pain information from the brain back to the periphery.
All components — ascending, central, and descending — are important.

- In actuality, it may be that the “wholeness” of the entire pain matrix is really the most important issue in pain (i.e., that symptoms of pain may result whenever there is damage anywhere within the circuit-like neural matrix).
- When a disruption of the pain matrix occurs, the circuit’s inherent modulatory systems also may come into play, further impacting pain.
- Chronic pain may trigger significant remodeling of neural structures within the circuitry of pain (next slide), so that the pain matrix itself changes over time.
Basal Ganglia:

- May be part of this pain-processing system, based on neuroimaging studies that documented the presence of acute bilateral basal ganglia lesions in uremic diabetic patients and the observation that these patients often develop hyperalgesia in addition to the anticipated Parkinson-like movement disorders.
The role of the basal ganglia in nociception and pain

- Eric H. Chudler and Willie K. Dong

- The basal ganglia (the striatum, globus pallidus and substantia nigra) also process non-noxious and noxious somatosensory information.

- Electrophysiological experiments agree that some neurons within the basal ganglia encode stimulus intensity.

- Many basal ganglia neurons responsive to somatosensory stimulation are activated exclusively or differentially by noxious stimulation.

- Indirect techniques used to measure neuronal activity (i.e., positron emission tomography and 2-deoxyglucose methods) also indicate that the basal ganglia are activated differentially by noxious stimulation.
The role of the basal ganglia in nociception and pain

- Microinjection of opiates, dopamine and gamma-aminobutyric acid (GABA) into the basal ganglia affects supraspinal pain behaviors more consistently than spinal reflexive behaviors.
- Pain behavior reduces electrical stimulation of the substantia nigra and caudate nucleus provides additional evidence for a role of the basal ganglia in pain modulation.
- Some patients with basal ganglia disease (e.g., Parkinson's disease, Huntington's disease) have alterations in pain sensation in addition to motor abnormalities. Frequently, these patients have intermittent pain that is difficult to localize.
The role of the basal ganglia in nociception and pain

- Collectively, these data suggest that the basal ganglia may be involved in the (1) sensory-discriminative dimension of pain, (2) affective dimension of pain, (3) cognitive dimension of pain, (4) modulation of nociceptive information and (5) sensory gating of nociceptive information to higher motor areas. Further experiments that correlate neuronal discharge activity with stimulus intensity and escape behavior in operantly conditioned animals are necessary to fully understand how the basal ganglia are involved in nociceptive sensorimotor integration.

• Hence, a noxious stimulus originating in the periphery travels through multiple transmission systems to reach various parts of the CNS. The CNS does not receive a noxious stimulus passively. Rather, it processes this stimulus using various regulatory mechanisms.
Several supraspinal centers are involved in processing and modulating pain signals, and can be divided into:
- subcortical and
cortical areas.

The subcortical areas most notably activated by pain signals include thalamus, basal ganglia, and cerebellum.

Commonly reported cortical areas include somatosensory cortices (SI and SII), anterior cingulate cortex and insular cortices, prefrontal cortex, and motor and pre-motor cortex.
PAG = group of neurons surrounding (peri) the cerebral aqueduct in the midbrain.

- Specifically, the somatosensory cortices have been implicated in interpreting sensory features of pain.
- The anterior cingulate cortex and insular cortices, both components of the limbic system, have been implicated in affective processing of pain.
- Moreover, prefrontal cortical areas, as well as parietal association areas, are also sometimes activated in response to noxious stimuli and may be related to cognitive variables, such as memory and stimulus evaluation.
- Motor and pre-motor cortical areas, also activated on occasion by pain stimuli, have been suggested to be related to pain epiphenomena, such as suppression of movement or actual pain evoked movements.

The brain imaging studies reviewed here indicate the cortical and sub-cortical substrate that underlies pain perception.

Instead of locating a singular “pain center” in the brain, neuroimaging studies identify a network of somatosensory (S1, S2, IC), limbic (IC, ACC) and associative (PFC) structures receiving parallel inputs from multiple nociceptive pathways (Fig. 1).

In contrast to touch, pain invokes an early activation of S2 and IC that may play a prominent role in sensory-discriminative functions of pain.
The strong affective-motivational character of pain is exemplified by the participation of regions of the cingulate gyrus. The intensity and affective quality of perceived pain is the net result of the interaction between ascending nociceptive inputs and antinociceptive controls.

Dysregulations in the function of these networks may underlie vulnerability factors for the development of chronic pain and comorbid conditions.

Elements of the pain network are best identified by hemodynamic imaging methods, while the temporal sequence and time delays to activating different cortical regions are best studied with EEG and MEG methods.
Brain regions involved in modulating pain perception seem identified best with studies involving neurotransmitter and neuroreceptor changes, although psychological modulation of pain is also being examined with fMRI, PET, and EEG/MEG studies.

There seems to be good evidence for somatotopic organization for pain representation in some brain areas, with divergent views when studied with hemodynamic methods or with EEG or MEG methods.

Experimental pain in normal subjects and chronic clinical pain conditions have distinct but overlapping brain activation patterns.

Studies in normal subjects tend to emphasize transmission through the spinothalamic pathway, which transmits afferent nociceptive information through Th to S1, S2, IC and ACC.
The primary brain areas accessed through this pathway decrease in their activation incidence in chronic clinical pain.

In contrast, the PFC activity seems to increase in incidence in clinical pain conditions.

Since pathways outside of the spinothalamic tract, such as spinoparabrachial, spinohypothalamic and spinoreticular projections, may activate PFC, nociceptive information transmission through those pathways may become more important in chronic clinical pain conditions.

A similar conclusion was arrived at by Hunt and Mantyh (2001) based on studying peripheral and spinal cord changes that accompany neuropathic pain-like behavior in rodents.
The preferential activation of PFC in clinical conditions suggests the simple hypothesis that chronic pain states have stronger cognitive, emotional, and introspective components than acute pain conditions.

Decreased incidence of activity across ACC, S1, S2, IC, and Th in chronic pain conditions as compared to brain activity for pain in normal subjects has been observed, (Derbyshire, 1999) (decreased incidence of ACC and Th in chronic pain in contrast to pain in normal subjects was also noted by Peyron et al., 2000).

Chronic pain conditions may be a reflection of decreased sensory processing and enhanced emotional/cognitive processing.

Craig et al. (1994, 1996) proposed that central pain may be a consequence of disinhibition within the spinothalamic pathway.
Fig. 1. Cortical and sub-cortical regions involved in pain perception, their inter-connectivity and ascending pathways. Locations of brain regions involved in pain perception are color-coded in a schematic drawing and in an example MRI. (a) Schematic shows the regions, their inter-connectivity and afferent pathways. The schematic is modified from Price (2000) to include additional brain areas and connections. (b) The areas corresponding to those shown in the schematic are shown in an anatomical MRI, on a coronal slice and three sagittal slices as indicated on the coronal slice. The six areas used in meta-analysis are primary and secondary somatosensory cortices (S1, S2, red and orange), anterior cingulate (ACC, green), insula (blue), thalamus (yellow), and prefrontal cortex (PF, purple). Other regions indicated include primary and supplementary motor cortices (M1 and SMA), posterior parietal cortex (PPC), posterior cingulate (PCC), basal ganglia (BG, pink), hypothalamus (HT), amygdala (AMYG), parabrachial nuclei (PB), and periaqueductal gray (PAG).

Fig. 2. Brain regions displaying different frequencies of activation between high- and low-sensitivity subgroups. Circles are centered on regions where the peak differences between groups were located. Colors in A and C correspond to the number of individuals displaying statistically significant activation at a given voxel (frequency), whereas colors in B and D correspond to the z-score of the subgroup analysis. Slice locations in A and B are ~2 mm from the midline, whereas slice locations in C and D are 32 mm from the midline (in standard stereotaxic space). Structural MRI data (gray) are averaged across all individuals involved in corresponding functional analysis.
CNS remodeling as a result of chronic pain:

- Flor and colleagues postulated that as a result of excessive nociceptive barrage, persistent painful stimulation might lead to cortical reorganization in patients with chronic back pain (CBP).21
- They used magnetoencephalography to study cortical pain response to electrical stimulation in 10 patients with chronic low back pain versus 10 matched controls.
- Among individuals suffering from a painful back, the brain’s cortical representation of the “back” area shifted medially, possibly indicating an expansion of the “back” representation to the neighboring “foot” and “leg” areas of the cortex.
Central Reorganization

Normal terminations of primary afferents in the dorsal horn

After nerve injury, C-fiber terminals atrophy and A-fiber terminals sprout into the superficial dorsal horn

- A-fibers normally terminate in the laminae of the dorsal horn.
- Peripheral nerve injury induces sprouting of A-fiber central terminals into lamina II (which normally receives nociceptor C-fibers innervation exclusively).
- This suggests that A-fibers sprouting into lamina II will begin to transmit information from non-noxious stimuli that may be interpreted as noxious and give rise to mechanical allodynia.
- Rewiring of synaptic connectivity may explain why patients with postherpetic neuralgia (and absent nociceptor innervation of the skin) experience tactile alldynia.
Regulation of Pain: Accentuation

- Passive transmission of noxious stimuli cannot explain how people experience pain.
- Rather, their pain experience can be explained by an active process.
- This active process includes several regulatory mechanisms that participate in attenuating or accentuating the perception of a noxious stimulus.
- An accentuated pain experience can be associated with factors such as edema, fear, anxiety, and release of endogenous chemicals that sensitize nerve endings.
- Spinal cord level mechanisms explain an accentuated pain experience:
  - 1) allodynia,
  - 2) wind-up, and
  - 3) central sensitization.
Allodynia

- It occurs when normally innocuous stimuli begin to produce pain.
- Following intense, repeated, or prolonged stimulation, or if inflammation is present,
  - the threshold for primary afferent nociceptors is lowered and
  - the frequency of firing is higher for all stimuli.
- Example: after a sunburn, light breeze may elicit pain

Lundy-Ekman, 2002, Chapter 7: Somatosensation
Wind-Up

- Example: frequently touching the hot plate becomes painful
- Low frequency repetitive stimulation of C-fibers produces a gradual increase in the discharge frequency of WDR neurons until they are in a state of nearly continuous discharge.
- In this state there are
  - augmented responses to input and
  - enlarged receptive fields.
  - Input from areas that previously did not activate the WDR neuron now evoke a prominent response, and
  - Low threshold stimulation is able to drive the neurons.
- Wind-up is elicited by any prolonged or intense C-fiber input.
Central Sensitization

- It results in an increased responsiveness of the nociceptive dorsal horn neurons resulting in enhanced conduction of pain signals to the brain.
- E.g.: following injury, an area of undamaged skin adjacent to the damaged tissue can evoke pain by either an
  - innocuous stimulus (secondary allodynia) or
  - more pain by a previously painful stimulus (secondary hyperalgesia).
- The nociceptors supplying area of secondary allodynia and hyperalgesia are not sensitized.
- However, central sensitization occurs due to input from nociceptors that supply an area of damage. Input from these nociceptors leads to a transient central sensitization.

Willis, Role of Neurotransmitters in Sensitization of Pain Responses, ANNALS NEW YORK ACADEMY OF SCIENCES
Central Sensitization

- Hardy, Woolf and Goodell (1967) provide a physiological explanation of this phenomenon.
- According to their model, active nociceptors produce pain signal, which in turn primarily activates the spinothalamic tracts (STT).
- These nociceptors also activate neural circuits in the spinal cord dorsal horn that also sensitize other STT cells that receive input from mechanoreceptors and nociceptors that supply an adjacent, but uninjured, region.
- Therefore, enhanced response of these STT cells to innocuous and noxious stimuli applied to uninjured skin results in secondary allodynia and hyperalgesia.

FIGURE 1. Diagram showing the possible central mechanisms underlying the pain, primary hyperalgesia, and secondary allodynia and hyperalgesia that follow application of a strong noxious stimulus to the skin. (From ref. 4, with permission.)
Wallenberg’s Syndrome

- Good example of how a single lesion in one portion of the pain matrix might lead to significant abnormal pain processing.
- In this condition, a lateral medullary infarct results in unilateral central pain, including allodynia (pain provoked by non-noxious stimulation) on the side of the body contralateral to the infarct, as well as contralateral hypoesthesia to noxious and thermal stimuli.
Neuroimaging showed:

- The neuropathic pain seen in Wallenberg’s syndrome might relate to an over-activated thalamus, which then hyper-amplified neural input to the higher pain centers, including Somatosensory cortex I and II, the insular cortex, and the anterior cingulate gyrus.
Medial Pain System:

- This suggestion that neuropathic pain might be related to increased input in the anterior cingulate and the insular cortex, as well as in SI and SII, is significant in light of theories regarding the affective versus discriminative components of pain.
- The anterior cingulate and the insular cortex are thought to be a part of the “medial pain system,” involved in generating the affective/emotional component of central pain.
Lateral Pain System

- The somatosensory cortex, SI and SII, and the parietal cortex have been postulated to be part of the “lateral” pain system, which is thought to be involved in the discriminative sensory components of pain.

- Although some evidence from neuroimaging studies lends credence to this medial-lateral distinction, there also is clinical evidence that individuals can have significant lesions in both of these pain systems and still experience neuropathic pain.
Ladarola’s PET studies of chronic pain:

• Compared to scans of pain-free normal subjects, the patients with neuropathic pain showed a statistically significant decrease in thalamic activity contralateral to the symptomatic side.
Hsieh’s PET study of rCBF in painful mononeuropathy.

• Increased activation in the insular, parietal, prefrontal, and cingulate cortices.

• Increased activity in the cerebellum, as well as in the temporal lobe.
Petrovic’s PET study of people with mononeuropathy and allodynia:

- Increased activation in the cerebellum and temporal lobes.
- Activations in SI and SII, midbrain, and other areas.
- Supported both the lateral (discriminatory) and medial (affective/emotional) pain systems being involved in the experience of allodynia in patients with neuropathy.
2 classic examples of pain attenuation.
- First, after injuring a hand, a person may shake it vigorously to reduce pain sensation.
- Second, an athlete, although injured during a game, may not feel injury related pain until end of game.

Regulatory mechanisms that attenuate pain act at four levels of the CNS:
- 1) the dorsal horn (DH; includes second order neurons of ascending pain pathways),
- 2) the descending fibers (from periaqueductal gray, raphe nuclei, and locus ceruleus),
- 3) hormonal system (cells located in the hypothalamus, pituitary gland, and adrenal medulla), and
- 4) cerebral cortex (prefrontal cortex, insular cortex, and amygdala).
• Mechanisms that attenuate pain at the dorsal horn (DH) have their basis in the gate control theory.
• According to the gate control theory, first order pain neurons (nociceptors) and second order pain neurons (WDR neurons) receive inhibitory signals from non-nociceptive A-β afferents.
• The A-β afferents are fast, myelinated, large diameter sensory peripheral nerves that arise from muscle spindles, golgi tendon organs, joint receptors or cutaneous tactile receptors.
• Increased activity of these fibers inhibits the WDR neurons in the DH, which are predominantly stimulated by the C fibers.
• Inhibition of the WDR neurons reduces pain signals reaching the brain, which reduces level of pain perceived, and, therefore attenuates pain experience.

Attenuation at Dorsal Horn

Fig. 4. Schematic diagram of the gate control theory of pain mechanisms: L, the large-diameter fibers; S, the small-diameter fibers. The fibers project to the substantia gelatinosa (SG) and first central transmission (T) cells. The inhibitory effect exerted by SG on the afferent fiber terminals is increased by activity in L fibers and decreased by activity in S fibers. The central control trigger is represented by a line running from the large-fiber system to the central control mechanisms; these mechanisms, in turn, project back to the gate control system. The T cells project to the entry cells of the action system. +, Excitation; −, inhibition (see text).

Melzack and Wall(1965), Science
Pain signals sent along acute and chronic pain fibres

Gate in spinal cord is open, so pain messages get through to the brain

Pain signals are still sent via acute and chronic pain fibres

The gate in the spinal cord is closed, so no pain messages get through to the brain

Rubbing the injury sends messages along touch and pressure fibres

Messages from touch and pressure fibres activate the gating nerve cell in the spinal cord
Attenuation by Descending Fibers

- Descending fibers also attenuate pain experience.
- The axons of the raphe nuclei, which receive information on noxious stimuli from periaqueductal gray, descend in the spinal cord via the dorsolateral funiculus. Their axons form the descending fibers that attenuate pain.
- These fibers attenuate pain experience by strongly inhibiting the second order pain neurons of the DH.
- This inhibition of the second order pain neurons reduces conduction of pain signals that travel from the periphery to the higher centers in the brain.
Attenuation by Hormonal System

• The action of β-endorphin (BE), which is formed by activity of the hypothalamo-pituitary-adrenocortical (HPA) axis, attenuates pain resulting from injury in situations such as accidents, disasters, or athletic contests.

• In such situations, an injured person may have a delayed onset of pain, i.e. pain begins at the end of an emergency or a contest. A delayed pain results partly because of BE that acts as a potent analgesic with its effect lasting a few hours.

• The release of BE from the HPA axis, in presence of noxious stimulus, can be explained by a group of neuronal projections. These projections include pathways ascending from the second order pain neurons in the DH of the spinal cord to the medial and lateral hypothalamus and several telencephalic regions, and pathways from the medullary reticular formation via the ventral noradrenergic bundle (VNB) to the periventricular gray of hypothalamus.
• The periventricular gray, which acts as the coordinating center of the HPA axis, responds to noxious stimuli (received from ascending pathways originating in the DH) by initiating a complex series of events regulated by feedback mechanisms.

• In response to noxious stimuli, the periventricular gray synthesizes and releases corticotropin-releasing hormone (CRH) into the portal circulation. This CRH stimulates the anterior pituitary gland to secrete several pro-opiomelanocortin derived neuropeptides into systemic circulation.

• These neuropeptides include adrenocorticotropic hormone (ACTH) and BE. BE binds with opiate receptors in the brain and the DH to result in analgesia.

• The amount of BE formed is regulated by ACTH, which stimulates the adrenal cortex to release corticosteroids such as hydrocortisone and corticosterone. These corticosteroids provide feedback to the regulatory processes by inhibiting the anterior pituitary, which represses the formation of pro-opiomelanocortin, thereby attenuating further secretion of BE and ACTH.
Chapman, 1995, Pain and Brain

FIG. 3. Schematic representation of feedback-mediated activation in the hypothalamic-pituitary-adrenocortical (HPA) axis. In response to afferent input, including noxious stimulation, the hypothalamic paraventricular nucleus (PVN) synthesizes corticotropin-releasing hormone (CRH), and secretes CRH into the portal circulation, thus stimulating the anterior pituitary. This leads to neurohypophyseal secretion of several pro-opiomelanocortin-derived neuropeptides, including adrenocorticotrophic hormone (ACTH), into the systemic circulation. ACTH stimulates the adrenal cortex to release corticosteroids such as hydrocortisone and corticosterone. Corticosteroids provide feedback to regulatory processes by inhibiting the anterior pituitary, and this represses pro-opiomelanocortin gene expression, thereby attenuating further ACTH secretion. Corticosteroid receptors exist on parvocellular PVN neurons, and in addition corticosteroids bind to the amygdala, hippocampus, and prefrontal cortical areas. In binding to the hippocampus and amygdala, corticosteroids initiate further inhibitory feedback to the hypothalamic PVN, and also restrain the activity of the locus coeruleus (LC). (-) = inhibition; (+) = excitation.
The cortical role in attenuating pain can be described in context of stimulation-produced analgesia (SPA).

SPA involves a highly specific suppression of behavioral responses to noxious stimuli produced by electrical stimulation of specific brain sites.
Attenuation by Cerebral Cortex

- Experimental SPA was first elicited by electrical stimulation of the periaqueductal gray in rodents.
- Upon this electrical stimulation, rodents remained alert and active, but their responses to noxious stimuli (orientation, vocalization and escape) were absent.
Attenuation by Cerebral Cortex

- An SPA-like response has been elicited in humans.
- Subsequent research has indicated that periaqueductal gray plays an important part in this analgesia.
Attenuation by Cerebral Cortex

- The periaqueductal gray receives afferents from brainstem, diencephalon, medial prefrontal cortex, limbic system insular cortex, and amygdala (that receives massive input from hippocampus and neocortex). The periaqueductal gray also projects efferents rostrally to the medial thalamus and orbital frontal cortex and the rostral ventromedial medulla (RVM).
Attenuation by Cerebral Cortex

- The periaqueductal gray integrates inputs from various afferents with ascending nociceptive inputs, and, in turn controls spinal nociceptive neurons through relays in the RVM.
- The RVM, which consists of the raphe nuclei and surrounding reticular nuclei, projects fibers to the DH to exert bidirectional control over nociceptive transmission. Bidirectional control by RVM involves both inhibitory and excitatory interneurons.
- The RVM has ‘off cells’ and ‘on cells.’ The increased activity of ‘off cells’ has an inhibitory effect, which attenuates pain by reducing activity of second order pain afferent neurons in the DH. However, the increased activity of ‘on cells’ has an excitatory effect, which accentuates pain by increasing activity of second order pain afferent neurons in the DH.
Acute Pain

- Acute pain has been defined as “pain associated with tissue damage, inflammation, or a disease process that is of relatively brief duration (i.e. hours, days, or even weeks), regardless of its intensity.”

- Acute pain results from
  - disease, inflammation, or injury to tissues.
  - Sudden onset e.g., after surgery or trauma
  - may be accompanied by anxiety or emotional distress

- The cause
  - can usually be diagnosed and treated
  - confined to a given period of time and severity
• Acute pain persists until healing takes place or stops long before healing has been completed.
• Healing can occur without medical intervention as an injury with acute pain does not overwhelm the body’s reparative mechanisms. Such healing usually takes a few days to a few weeks, and therefore acute pain lasts for the same duration.
• Additionally, acute pain has been associated with anxiety. The clinical observation that greater the anxiety the greater the perception of an injury as painful appears warranted. However, a clear empirical basis for this simple proposition does not exist. Different studies indicate that anxiety enhances, relieves or has no impact on pain.
Chronic Pain

• Chronic pain has been defined as “pain that persists for extended periods of time (i.e. months or years), that accompanies a disease process (e.g. rheumatoid arthritis), or that is associated with an injury that has not resolved within an expected period of time (e.g. myofascial pain syndromes, complex regional pain syndrome, and chronic pelvic pain).”

• Chronic pain is widely believed to represent *disease* itself
  – It can be made much worse by unpleasant environmental and psychological factors.
  – It persists over a longer period of time than acute pain
  – It is *resistant to most medical treatments*
  – It causes severe problems for the patient
• Chronic pain indicates that the pain has lost its biological role of triggering recuperative behavior.

• Chronic pain, although triggered by injury or disease, however, has other factors associated with it that prolong its presence. These factors include continued tissue damage, loss of a body part, extensive trauma, or damage to the nervous system as a result of injury.

• Due to these factors, the pain persists either beyond the expected course of disease, or beyond the time expected for an injury to heal, or it recurs at various times for months or years. In such situations, the injury may exceed the body’s capability to heal. Additionally, intensity of chronic pain may be out of proportion of original injury or damage, and syndromes, such as complex regional pain syndrome, may occur spontaneously without any signs of injury.

• Chronic pain impairs an individual’s social, vocational and psychological well being. Among psychological factors, chronic pain has been frequently associated with depression, which may vary from minor to severe.

• Depression also appears to intensify chronic pain. While some patients display depression, others maintain a dispassionate attitude. Patients with a dispassionate attitude appear to have either strong personal or social resources or the pain disorder provides a focus in life that enables them to ignore stressful life challenges, thereby controlling depression.
Gray Matter Loss in Chronic Pain

- Fibromyalgia is an intractable widespread pain disorder that is most frequently diagnosed in women.
- Fibromyalgia patients demonstrated significantly less gray matter density than healthy controls in several brain regions, including the cingulate, insular and medial frontal cortices, and parahippocampal gyri.

The Journal of Neuroscience, April 11, 2007 • 27(15):4004–4007
Gray Matter Loss in Chronic Pain

- Patients with Chronic Back Pain (CBP) showed 5–11% less neocortical gray matter volume than control subjects.
- Gray matter density was reduced in bilateral dorsolateral prefrontal cortex and right thalamus.

The Journal of Neuroscience, November 17, 2004 • 24(46):10410 –10415
Referred Pain

Referred pain

Sensory neurone from internal organ

Brain interprets messages as coming from the skin

Pain signals

Pain signals sent to the brain

Sensory neurone from the skin becomes activated, indirectly

Sensory neurone from the skin synapses with the same spinal neurone from the damaged organ
# Pain

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