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Pathophysiology of pain

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Pain is the most common complaint that is debilitating, and affects the individual person, their families, and time loss at work. Over 100 million Americans suffer from chronic pain and 63% of the patient seeks help initially from their primary care Physician.[1] According to 2010 survey, 19% adults in USA report constant or frequent pain persisting for at least 3 months.[2]

Persistent pain often causes functional impairment and disability, psychological distress, anxiety, depression, and sleep deprivation. Pain disrupts activities of daily living and personal relationships.[3] Pain is the most common cause of long-term disability, with lost work days.

Definition of pain

Pain is an unpleasant sensory and emotional experience associated with actual and or potential tissue damage or described in terms of such damage.[4]

According to the time course and duration, pain can be classified into an acute and chronic pain.

Acute pain

Acute pain is the normal predicted physiological response to an adverse chemical, thermal, or mechanical stimulus. It results from activation of the pain receptors (nociceptors) at the site of tissue damage. This type of pain usually accompanies surgery, traumatic injury, tissue damage, and inflammatory process. Acute pain plays a vital role in providing warning signals that something is wrong and is in need of further examination. It is self-limiting and resolves over days to weeks, but it can persist longer as healing occurs. Acute pain can activate the sympathetic branch of the autonomic nervous system and produce such response as hypertension, tachycardia, diaphoresis, shallow respiration, restlessness, facial grimacing, guarding behavior, pallor, and pupil dilation. Pain in response to tissue damage is a normal phenomenon, it may be associated with significant, unnecessary physical, psychological, and emotional distress. Inadequately controlled pain can be a factor in the development of chronic pain.

Chronic pain

Chronic pain generally refers to intractable pain that exits for 3 or more months and does not resolve in response to treatment.[5] Chronic pain can be viewed as its own disease than as a

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symptom of another health problem. It can be affected by physical, environmental, and psychological factors. Chronic pain may reduce quality of life, well-being, and ability to function over the long-term. In chronic pain, positive adaptation does not occur, as time passes the pain system become more sensitive, hyperresponsive and able to produce intense, spreading and unremitting pain. Chronic pain does not resolve on its own and require specialized knowledge from the health care professionals and often require a team of health care professional and interdisciplinary treatment approach. Chronic pain also necessitates treatment of the hypersensitive nervous system, based on our understanding of pain neuroscience, biopsychological perspective, and neuroplasticity. Chronic pain may originate in the body, or in the brain, or spinal cord. It is difficult to treat chronic pain but some people may benefit from the opioid management but others do not. Various non-opioid medications are also used such as the neuropathic medications for the treatment of the psychological component of the pain. Psychological and the behavioral therapy have shown effective for improving quality of life in those with chronic pain.

Pain descriptor terminology[6]

Hyperalgesia: increased response to a stimulus that normally is painful.
Hypoalgesia: diminished response to normally painful stimuli.
Analgesia: absence of pain in response to stimulation that normally is painful.
Hyperesthesia: increased sensitivity to stimulation.
Hypesthesia: diminished sensitivity to stimulation.
Dysesthesia: an unpleasant abnormal sensation, spontaneous, or evoked.
Paresthesia: an abnormal sensation, spontaneous, or evoked.
Allodynia: pain resulting from a stimulus (such as light touch) that does not normally elicit pain.[7]

Classification of pain

Pain can be classified according to the neurophysiological mechanism, temporal aspects, etiology, or region affected.

Neurophysiological mechanism of pain has been categorized as nociceptive and non-nociceptive pain.

Nociceptive pain

Nociceptive pain is presumed to be maintained by continual tissue injury, it results from the activation or sensitization of nociceptors in the periphery, which transduce noxious stimulus into electrochemical impulse. These impulses are then transmitted to the spinal cord and higher rostral centers in the central nervous system. Nociceptive pain is sub-divided into somatic and the visceral pain.[8]

Somatic pain

Results from excitation and sensitization of nociceptors in tissues, such as bone, peripheral soft tissue, joints, and muscles. Somatic pain is characterized, as well localized typographically. It is intermittent or constant and is described as aching, stabbing, gnawing, or throbbing. There are five physiological processes involved in the somatic nociception.

i. *Transduction*: noxious stimuli (mechanical, chemical, and thermal) act on peripheral nociceptors and are converted into electrical activity, hence, culminating in an action potential. This is carried as a nerve impulse.
ii. *Conduction*: nerve impulse travels through the length of the first order neurons to reach the synapse with the second order neuron.

iii. *Transmission*: synaptic transfer of information takes place at the synapse between the first and the second order neurons in the dorsal horn of the spinal cord.
iv. *Perception*: the actual conscious experience of the pain, both sensory (localization, character, and discrimination) and affective (emotional) aspect.
v. *Modulation*: pain experience is not a direct and proportionate mechanical response to the noxious stimuli. A multitude of factors modulate the stimulus–response pathway.

Visceral pain

Visceral pain has five important characteristics:

i. Visceral organs are not sensitive to pain.
ii. It is not always linked to visceral injury (cutting the intestine cause no pain, but stretching of the bladder cause pain).
iii. It is diffuse and poorly localized.
iv. It is referred to other locations.
v. It is accompanied by motor and autonomic reflexes such as nausea and vomiting.

Non-nociceptive pain

Non-nociceptive pain can be sub-divided into neuropathic and idiopathic pain.

Neuropathic pain

Neuropathic pain can result from injury to neural structures within the peripheral and central nervous system. It is believed to be caused by aberrant somatosensory processing in the central and the peripheral nervous system. Neuropathic pain is usually sharp and burning. There are three subset of neuropathic pain.

i. Peripherally mediated involve the peripheral nerves, brachial plexus.
ii. Central pain syndrome involves the nervous system.
iii. Sympathetically mediated pain that can be generated centrally and peripherally, like RSD symptoms.

Idiopathic pain

Idiopathic pain is used interchangeably with the psychogenic pain. Idiopathic pain is more appropriate as it implies broad spectrum of poorly understood pain states such as myofascial pain syndrome and somatization pain disorder.

Pain pathways

Ascending pathway has three neuron pathways.[9]

i. *First order neuron*: start from the periphery (skin, bone, ligaments, muscles, and other viscera) travels through the peripheral nerve, reaches dorsal horn of the spinal cord.
ii. *Second order neuron*: start at the dorsal horn cross over to the contralateral side and then ascent in the spinal cord to the thalamus, and other brain areas like dorsolateral pons.
iii. *Third order neuron*: (also called tertiary neuron) starts at the thalamus and then terminates in the cerebral cortex.

Descending pathway: start at the brain area of Limbic System, parabrachial area (PBA), periaqueductal grey (PAG) nucleus raphe Magnus, and rostral ventromedial medulla.

Types of afferent nerve fibers

There are three types of primary afferent sensory nerve fibers, A-beta, and A-delta and C fibers.[10]

1. A-beta fibers are myelinated fibers with a diameter of 6-12 μm, the conduction speed is 30–50 m/s, stimulation threshold is low and activated by touch and vibration. Typically these fibers do not carry pain sensation; however, in neuropathic pain they carry pain and unpleasant sensations.
2. A-delta fibers: they are thinly myelinated, diameter of 2-5 μm, speed 2–25 m/s. Threshold for stimulation is high and are activated by noxious stimuli, transmit pain faster than the unmyelinated C fibers, and initiate the reflex response.
3. *C-fibers*: unmyelinated fibers, high threshold, diameter of 0.2-1.5 μm, with a speed of < 2 m/s. They are activated by noxious stimuli, carry pain sensation from the periphery to the center. Stimulation cause a delayed perception of pain described as a diffuse burning, stabbing, and sensation.

Theories of pain

There are several theories of the pain. Four of them are usually more acceptable which are specificity, intensity, pattern, and gate control theories of pain.[11]

Specificity theory of pain

The fundamental thought process behind this theory as the name implies is that each modality has a specific receptor and associated sensory fiber (primary afferent) that is sensitive to one specific stimulus.

For example non-noxious and noxious stimulus, stimulate the low threshold mechanoreceptors or the nociceptors, respectively. Then travel through the primary afferent to the second order neurons in the spinal cord or brain stem. The second order neuron reached the higher centers of the brain or the pain centers in the brain. This theory has been tested and postulated in 19th century in Western Europe.[12]

Intensity theory of pain

Intensive or summation theory is now referred to as the intensity theory and has been postulated several times in history. Initially described by a scientist Plato in fourth century BC “as pain is not a unique sensory experience but rather, an emotion that occur when a stimulus is stronger than usual.”

Later in 17th century, Erasmus Darwin reiterated this concept. Almost century after that Wilhelm Erb also suggested that pain occurs if the intensity reaches to a certain threshold in a sensory system.

Arther Goldscheider further made advances in the theory based on the experiment by Bernhard Naunyn in 1859 on the syphilis patients. He demonstrated that repeated tactile stimulation below the threshold for tactile perception produce pain with degenerating dorsal columns in those patients.[13] It was postulated that there must be some form of summation that occur at a sub-threshold level that cause unbearable pain. It was also suggested during that work that increased sensory input would converge and summate in the grey matter of the spinal cord.

Pattern theory of pain

J.P. Nafe narrated a quantitative theory of feeling.

The theory stated that any somaesthetic sensation occurred by a specific and particular pattern of neural firing and that the spatial and temporal profile of firing of the peripheral nerves

encoded the stimulus type and intensity. According to the theory skin fiber endings except the one innervating the hair cells are identical and that the pain is produced by intense stimulation of these fibers.[14]

In 1953, Willen Noordenbos postulated that large fibers (touch, pressure, and vibration) may inhibit the signals carrying by the small C fibers. Pain intensity changes with the ratio of the large fibers to the small fibers.

Gate control theory of pain

Ronald Melzack[15] and Charles Patrick wall in 1965 proposed a theory that changed and revolutionized the research related to the pain; the theory is called gate control theory of pain that supported the specificity and the pattern theory.

Melzack and Wall accepted that there are nociceptive fibers, i.e., pain fiber and touch fibers. These fibers synapse in three different regions in the dorsal horn of the spinal cord.

1. Substantial gelatinosa
2. Dorsal column
3. Transmission cells

According to their theory the gates in the spinal cord are the substantial gelatinosa in the dorsal horn. These modulate the transmission of sensory information from the primary afferent neurons to the transmission cells in the spinal cord. The gating mechanism is controlled by the activity in the small and large fibers. Large fibers activity inhibits (or closes) the gate, whereas small fiber activity facilitates or opens the gate. Activity from descending fibers that originate in the supraspinal regions and travels to the dorsal horn could also modulate this gate. When nociceptive information reaches a threshold that exceeds the inhibition elicited, it opens the gate and activates the pathways that lead to the experience of the pain.

According to the gate theory activation of the nerve fibers, which do not transmit pain signals called, non-nociceptive fibers. There is further explanation of the fiber. There are two types of afferent pain receptive nerves that bring the signals to the brain. A fast, relatively thick, myelinated A-delta fibers that carries messages quickly with intense pain and small unmyelinated slow C fibers that carries the long-term throbbing and chronic pain. Large diameter A-beta fibers and non-nociceptive do not transmit pain stimuli and inhibit the effect of firing by A-delta and C-fibers.[16]

Dorsal horn of the spinal cord is involved in receiving pain stimuli from A-delta and C-fibers, called Laminae, which also receives input from A-beta fibers. Non-nociceptive fibers indirectly inhibit the effect of the pain fibers “closing the gate” and interrupt the transmission of pain. In other parts of the Laminae, pain fibers also inhibit the effects of non-nociceptive fibers, “opening the gate.”

This pre-synaptic inhibition of the dorsal nerve endings can occur through specific Type of GABA a receptors and not through the glycine receptors. Certain type of GABA a receptors subtypes can pre-synaptically regulate Nociception and pain transmission. Gate control theory explains how stimulus that activates only non-nociceptive nerves can inhibit the firing of nociceptive pain.

Area of the brain involved in reduction of pain sensation is the periaqueductal gray matter that surrounds the third ventricle and the cerebral aqueduct of the ventricular system. Stimulation of this area produces analgesia by activating descending pathways that directly and indirectly inhibit nociceptors in the Laminae of the spinal cord. Descending pathways also activate opioid receptor, which contains parts of the spinal cord.

Afferent pathways interfere with each other, so the brain can control the degree of pain that is perceived, based on which pain stimuli are to be ignored to pursue potential gains. The brain determines which stimuli are profitable to ignore over time. Thus the brain controls the perception of pain quite directly and can be trained to turn off forms of pain that are not useful.

That understanding led Melzack to assert that pain is in the brain. There was skepticism when it is first proposed in 1965 despite several modifications; its basic conception remains unchanged.

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