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PHYSIOLOGY OF PAIN

Methodical manual for students



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Students' independent practical work is an important part of the syllabus in the course of Normal Physiology. It helps students to study this fundamental subject.

Systematic independent work enables to reach the final goal in the students' education. It is also important while preparing the students for their future clinical work with patients.

These lectures, questions and tests will help students to get ready for the examination.

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Theme actuality, study purposes, concrete purposes of the module

Pain is an unpleasant feeling that is an essential component of the body's defense system. It provides a rapid warning to the nervous system to initiate a motor response to minimize physical harm. Lack of the ability to experience pain, as in the rare condition congenital insensitivity to pain with anhidrosis (Axelrod and Hilz 2003), can cause very serious health problems. Pain is the most common reason for physician consultation in most advanced countries. It is a major symptom in many medical conditions, and can significantly interfere with a person's quality of life and general functioning. Understanding the regulation of the physiology of pain necessary in the practice of every physician.

Study purposes: to know the physiology of pain and pain modulation.

Concrete purposes of the module:

A student must know:

- Pain Principles;
- Pain Tracts and Sources;
- Processing of nociceptor signals in the spinal cord;
- Pain Modulation.

Introduction

Pain is a vital function of the nervous system in providing the body with a warning of potential or actual injury. It is both a sensory and emotional experience, affected by psychological factors such as past experiences, beliefs about pain, fear or anxiety.

This article provides an overview of the physiological mechanisms of pain and the important pain pathways. We will discuss pain receptors, transmission of pain signals to the spinal cord and pain pathways within the spinal cord. We will also look at how pain can be modulated at different levels along the pathway. Finally we discuss different types of pain including visceral and neuropathic pain.

Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage (IASP – International Association for the Study of Pain 2011)

Pain Principles

Most of the sensory and somatosensory modalities are primarily informative, whereas pain is a protective modality. Pain differs from the classical senses (hearing, smell, taste, touch, and vision) because it is both a discriminative sensation and a graded emotional experience associated with actual or potential tissue damage.

Pain is a submodality of somatic sensation. The word "pain" is used to describe a wide range of unpleasant sensory and emotional experiences associated with actual or potential tissue damage. Nature has made sure that pain is a signal we cannot ignore. Pain information is transmitted to the CNS via three major pathways (Figure 1.1).

Most ailments of the body cause pain. The ability to diagnose different diseases depends to a great extent on the knowledge of the different qualities and causes of pain. Sensitivity and reactivity to noxious stimuli are essential to the well-being and survival of an organism. Pain travels through redundant pathways, ensuring to inform the subject: “Get out of this situation immediately.” Without these attributes, the organism has no means to prevent or minimize tissue injury. Individuals congenitally insensitive to pain are easily injured and most of them die at an early age.

For thousands of years, physicians have tried to treat pain without knowing the details of the ways in which pain is signaled from the injured part of the body to the brain, or the ways in which any of their remedies worked. Recent discoveries about how the body detects, transmits and reacts to painful stimuli, have allowed physicians to relieve both acute and chronic pain.

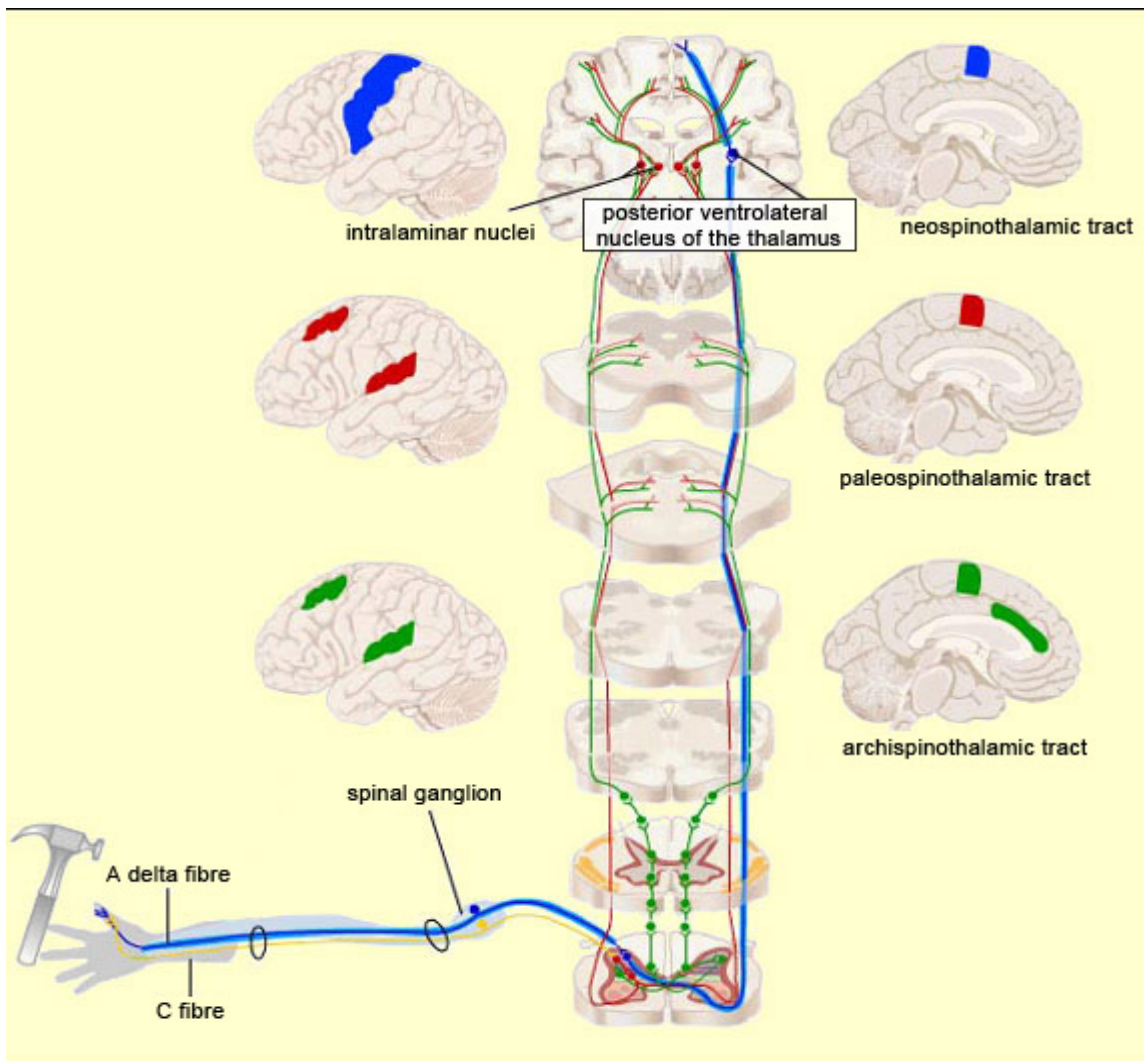


Figure 1.1 Three pathways carrying pain sensation from the periphery to the central nervous system.

1.1. Pain Receptors

Pain is termed nociceptive (nocer – to injure or to hurt in Latin), and nociceptive means sensitive to noxious stimuli. Noxious stimuli are stimuli that elicit tissue damage and activate nociceptors.

Nociceptors are sensory receptors that detect signals from damaged tissue or the threat of damage and indirectly also respond to chemicals released from the damaged tissue. Nociceptors are free (bare) nerve endings found in the skin, muscle, joints, bone and viscera. Recently, it was found that nerve endings contain transient receptor potential (TRP) channels that sense and detect damage. The TRP channels are similar to voltage-gated potassium channels or nucleotide-gated channels, having 6 transmembrane domains with a pore between domains 5 and 6. They transduce a variety

of noxious stimuli into receptor potentials, which in turn initiate action potential in the pain nerve fibers. This action potential is transmitted to the spinal cord and makes a synaptic connection in lamina I and/or II. The cell bodies of nociceptors are mainly in the dorsal root and trigeminal ganglia. No nociceptors are found inside the CNS.

Nociceptors are not uniformly sensitive. They fall into several categories, depending on their responses to mechanical, thermal, and/or chemical stimulation liberated by the damage, tumor, and/or inflammation.

Skin Nociceptors. Skin nociceptors may be divided into four categories based on function. The first type is termed high threshold mechanonociceptors or specific nociceptors. These nociceptors respond only to intense mechanical stimulation such as pinching, cutting or stretching. The second type is the thermal nociceptors, which respond to the above stimuli as well as to thermal stimuli. The third type is chemical nociceptors, which respond only to chemical substances (Figure 6.2). A fourth type is known as polymodal nociceptors, which respond to high intensity stimuli such as mechanical, thermal and to chemical substances like the previous three types. A characteristic feature of nociceptors is their tendency to be sensitized by prolonged stimulation, making them respond to other sensations as well.

Joint Nociceptors. The joint capsules and ligaments contain high-threshold mechanoreceptors, polymodal nociceptors, and "silent" nociceptors. Many of the fibers innervating these endings in the joint capsule contain neuropeptides, such as substance P (SP) and calcitonin gene-related peptide (CGRP). Liberation of such peptides is believed to play a role in the development of inflammatory arthritis.

Visceral Nociceptors. Visceral organs contain mechanical pressure, temperature, chemical and silent nociceptors. The visceral nociceptors are scattered, with several millimeters between them, and in some organs, there are several centimeters between each nociceptor. Many of the visceral nociceptors are silent. The noxious information

from visceral organs and skin are carried to the CNS in different pathways (Figures 1.2).

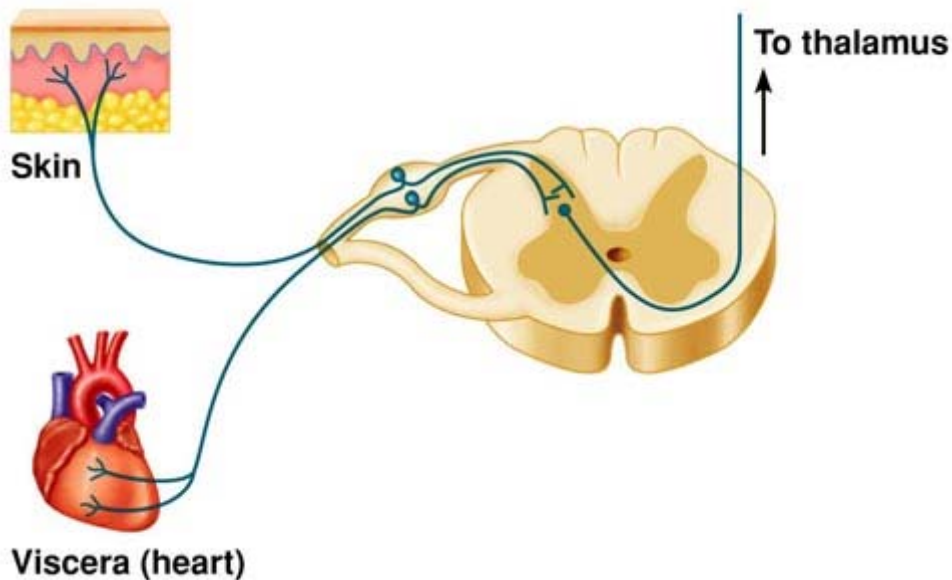


Figure 1.2 Visceral nociceptors and the fibers and pathways carrying the noxious information to the CNS.

Silent Nociceptors. In the skin and deep tissues there are additional nociceptors called "silent" or "sleep" nociceptors. These receptors are normally unresponsive to noxious mechanical stimulation, but become “awakened” (responsive) to mechanical stimulation during inflammation and after tissue injury. One possible explanation of the "awakening" phenomenon is that continuous stimulation from the damaged tissue reduces the threshold of these nociceptors and causes them to begin to respond. This activation of silent nociceptors may contribute to the induction of hyperalgesia, central sensitization, and allodynia (see below). Many visceral nociceptors are silent nociceptors.

Activation of the nociceptor initiates the process by which pain is experienced, (e.g., we touch a hot stove or sustain a cut). These receptors relay information to the CNS about the intensity and location of the painful stimulus.

1.2. Factors that Activate Nociceptors

Nociceptors respond when a stimulus causes tissue damage, such as that resulting from cut strong mechanical pressure, extreme heat, etc. The damage of tissue results in a release of a variety of substances from lysed cells as well as from new substances synthesized at the site of the injury (Figure 1.3). Some of these substances activate the TRP channels which in turn initiate action potentials. These substances include:

1. ***Globulin and protein kinases***. It has been suggested that damaged tissue releases globulin and protein kinases, which are believed to be amongst the most active pain-producing substances. Minute subcutaneous injections of globulin induce severe pain.
2. ***Arachidonic acid***. Arachidonic acid is one of the chemicals released during tissue damage. It is then metabolized into prostaglandin (and cytokines). The action of the prostaglandins is mediated through a G protein, protein kinase A cascade. The prostaglandins block the potassium efflux released from nociceptors following damage, which results in additional depolarization. This makes the nociceptors more sensitive. Aspirin is an effective pain killer because it blocks the conversion of arachidonic acid to prostaglandin.
3. ***Histamine***. Tissue damage stimulates the mast cells to release histamine to the surrounding area. Histamine excites the nociceptors. Minute subcutaneous injections of histamine elicit pain.
4. ***Nerve growth factor (NGF)***. Inflammation or tissue damage triggers the release of NGF. NGF then binds to TrkA receptors on the surfaces of nociceptors leading to their activation. Minute subcutaneous injections of NGF elicit pain.

5. ***Substance P (SP) and calcitonin gene-related peptide (CGRP)*** are released by injury. Inflammation of tissue damage also results in SP and CGRP release, which excites nociceptors. Minute subcutaneous injection of substance P and CGRP elicits pain. Both peptides produce vasodilation, which results in the spread of edema around the initial damage.

6. ***Potassium - K^+*** . Most tissue damage results in an increase in extracellular K^+ . There is a good correlation between pain intensity and local K^+ concentration.

7. ***Serotonin (5-HT), acetylcholine (ACh), low pH (acidic) solution, and ATP***. These substances are released with tissue damage. Subcutaneous injections of minute quantities of these products excite nociceptors.

8. ***Muscle spasm and lactic acid***. Not only can some headaches result from muscle spasms of smooth muscle, stretching of a ligament can also elicit pain. When muscles are hyperactive or when blood flow to a muscle is blocked, lactic acid concentration increases and pain is induced. The greater the rate of tissue metabolism, the more rapidly the pain appears. Minute subcutaneous injections of lactic acid excite nociceptors.

The release of these substances sensitizes the nociceptors (C fibers) and reduces their threshold. This effect is referred to as peripheral sensitization (in contrast to central sensitization that occurs in the dorsal horn).

Within 15-30 seconds after injury, an area of several cm around the injured site shows reddening (caused by vasodilation) called a flare. This response (inflammation) becomes maximal after 5-10 minutes, and this region shows a lowered pain threshold (i.e., hyperalgesia).

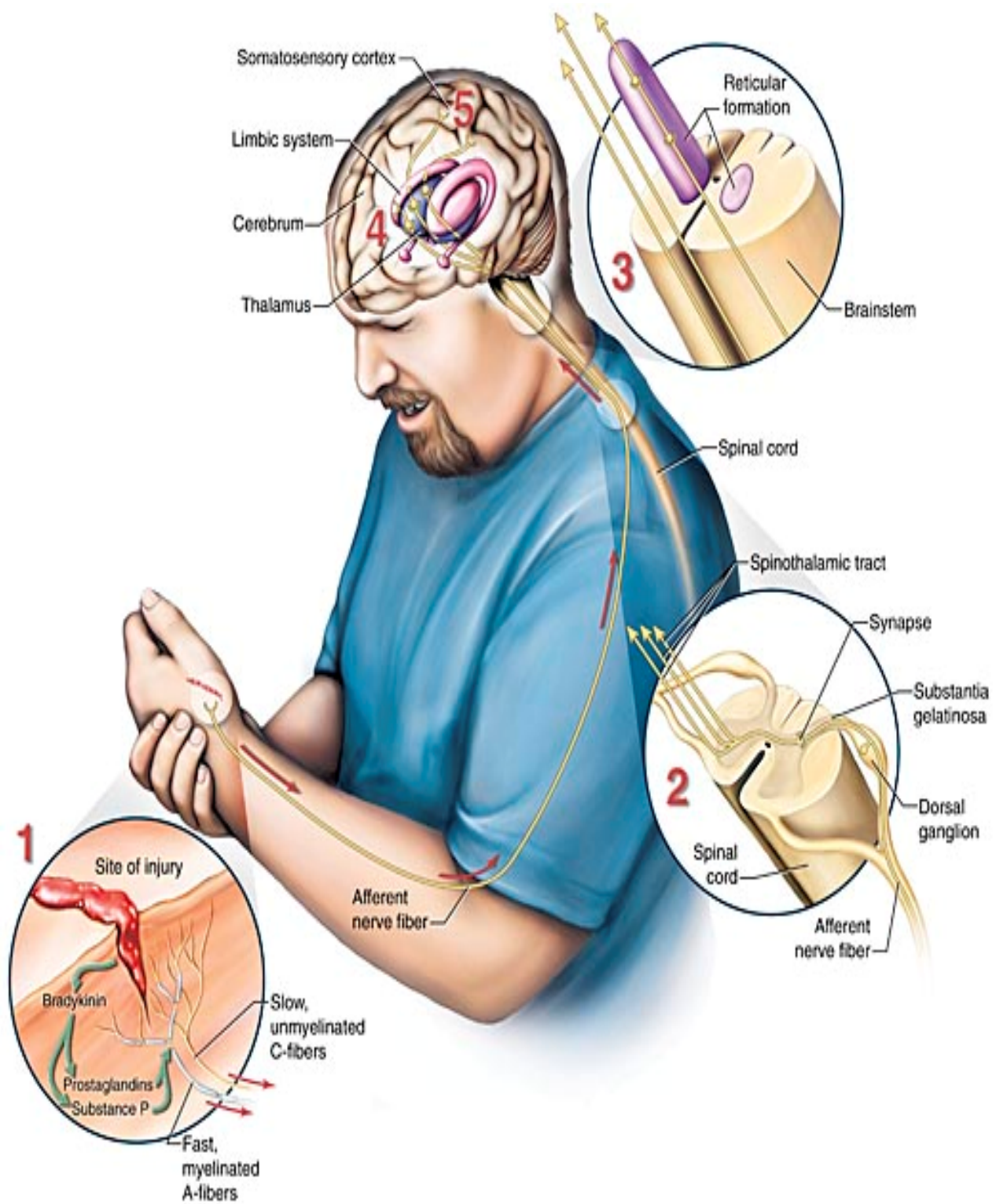


Figure 1.3 Tissue damage and the variety of the substances released from the injury site that activate the nociceptors.

Hyperalgesia. Hyperalgesia is an increased painful sensation in response to additional noxious stimuli. One explanation for hyperalgesia is that the threshold for pain in the area surrounding an inflamed or injured site is lowered. An additional explanation is that the inflammation activates silent nociceptors and/or the damage elicits ongoing nerve signals (prolong stimulation), which led to long-term changes and sensitized nociceptors. These changes contribute to an amplification of pain or hyperalgesia, as well as an increased persistence of the pain. If one pricks normal skin with a sharp probe, it will elicit sharp pain followed by reddened skin. The reddened skin is an area of hyperalgesia.

Allodynia. Allodynia is pain resulting from a stimulus that does not normally produce pain. For example, light touch to sunburned skin produces pain because nociceptors in the skin have been sensitized as a result of reducing the threshold of the silent nociceptors. Another explanation of allodynia is that when peripheral neurons are damaged, structural changes occur and the damaged neurons reroute and make connection also to sensory receptors (i.e., touch-sensitive fibers reroute and make synaptic connection into areas of the spinal cord that receive input from nociceptors).

In conclusion, the several kinds of endogenous chemicals are produced with tissue damage and inflammation. These products have excitatory effects on nociceptors. However, it is not known whether nociceptors respond directly to the noxious stimulus or indirectly by means of one or more chemical intermediaries released from the traumatized tissue.

1.3. Pain Thresholds and Just Noticeable Differences

Exposing the skin to controlled heat (produced by heating element or laser) makes it possible to measure the threshold for pain. When the temperature of the skin reaches $45 \pm 1^\circ\text{C}$, subjects report pain. Non-noxious thermal ($< 45^\circ\text{C}$) receptors are innervated by different types of nerve fibers than those responding to the pain. A temperature of approximately 45°C denaturates tissue protein and elicits damage in all subjects. That is,

the pain threshold in all subjects is about the same. However, the response to pain is different among people.

Pain is measured by the degree of pain intensity. Different degrees of pain intensity are defined as Just Noticeable Differences (JND). There are 22 JND for pain elicited by heat to the skin. This discrimination is possible because the discharge frequency of the nociceptors increases with increasing skin temperature. Thus, nociceptors also supply information on the stimulus intensity (intensity coding) in addition to the injury location.

1.4. Pain Fibers

The cell bodies of the primary afferent pain neurons from the body, face, and head are located in the dorsal root ganglia (DRG) and in the trigeminal ganglia respectively. Some of these cell bodies give rise to myelinated axons (A delta fibers), and others give rise to unmyelinated axons (C fibers). The free nerve endings arise from both A delta fibers and the unmyelinated C fibers, which are scattered together (Figure 1.4).

A delta fibers (group III fibers) are 2-5 mm in diameter, myelinated, have a fast conduction velocity (5-40 meters/sec), and carry information mainly from the nociceptive-mechanical or mechanothermal-specific nociceptors. Their receptive fields are small. Therefore, they provide precise localization of pain. C fibers (group IV fibers) are 0.4-1.2 mm in diameter, unmyelinated, have a slow conduction velocity (0.5-2.0 meters/sec), and are activated by a variety of high-intensity mechanical, chemical and thermal stimulation and carry information from polymodal nociceptors. C-fibers comprise about 70% of all the fibers carrying noxious input. Two classes of C-fibers have been identified. The receptive field of these neurons is large and, therefore, less precise for pain localization. Upon entering the spinal cord, the pain fibers bifurcate and ascend and descend to

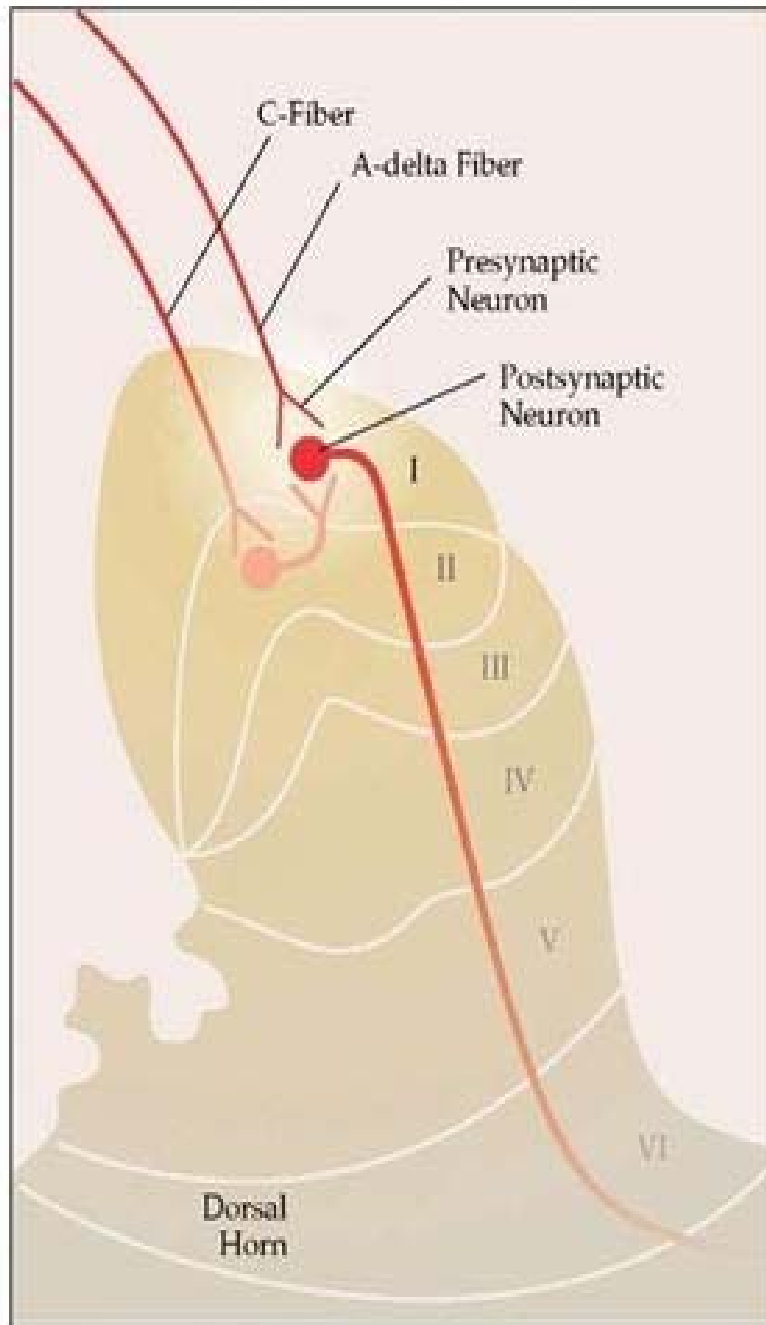


Figure 1.4 Conduction of noxious information via A delta and C fibers.

several segments, forming part of the tract of Lissauer before synapsing on neurons on Rexed layers I to II. In general, nociceptors responding to noxious stimuli transmit the information to the CNS via A delta fibers, which make synaptic connections to neurons in Rexed layer I (nucleus posterior marginalis). The nociceptors responding to chemical

or thermal stimuli (i.e., the polymodal nociceptors) carry their activity mainly by C unmyelinated fibers. One class of C fibers terminates in Rexed layer I, and the second class terminates in Rexed layer II (substantia gelatinosa). These fibers release substance P, glutamate, aspartate calcitonin gene related peptide (CGRP), vasoactive intestinal polypeptide (VIP), and nitric oxide.

1.5.Double Pain Sensations

Two sequential pain sensations in short time intervals is the result of sudden painful stimulation. The first one is immediately after the damage. It is followed several seconds later with additional pain sensation. These two separate sensations are several seconds apart because a fast transmitting information sensation is carried via A delta fibers and is followed several seconds later with slow transmitting pain information carried via C fibers. This phenomenon is known as “double pain sensation” (Figure 1.5).

Two experimental procedures were used to verify which information is carried by which fibers.

1. Externally applied pressure, such as compression of the skin above a nerve, first blocks the myelinated A delta fibers, while C fibers continue to conduct action potentials and allow the slow conducting pain to be carried.
2. A low dose of local anesthesia applied to peripheral nerves blocks the unmyelinated C fibers before the myelinated A delta fibers. Under this condition, the slow conducting pain information is blocked, and only the fast conducting pain information by A delta fibers is carried to the CNS. This experiment provides additional evidence that two different types of nerve fibers carry noxious information.

1.5.

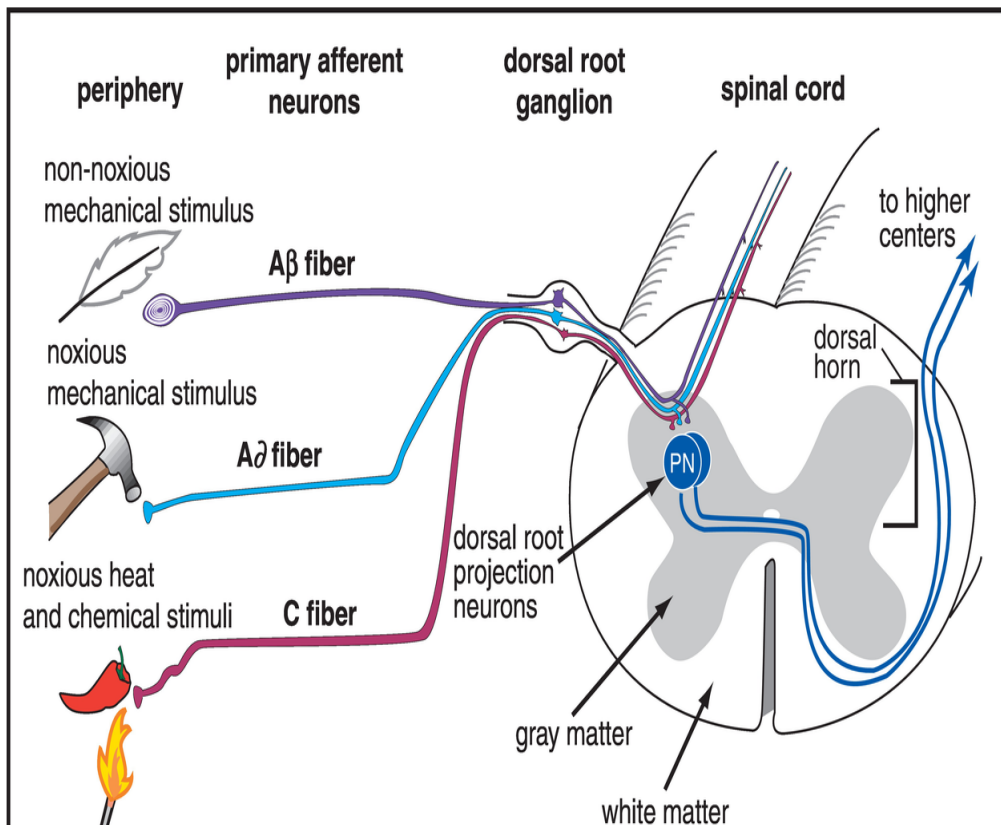


Figure 1.5 Conduction of noxious information via A delta and C fibers.

The synaptic terminals of the axons of the dorsal root ganglion, which carry noxious information arriving to Rexed layers I and II (Figure 1.6), release neurochemical agents such as substance P (SP), glutamate, aspartate, vasoactive intestinal peptide (VIP), cholecystokinin (CCK), somatostatin, calcitonin gene-related peptide (CGRP), galanin, and other agents. These agents activate the nociceurons. It was shown that when SP and CGRP are applied locally within the spinal cord dorsal horn, glutamate is released. The release of glutamate excites the nociceurons. Furthermore, SP receptors (neurokinin receptors) and NMDA receptors (glutamate) interact which result that the NMDA receptors will become more sensitive to glutamate, which results in central sensitization. The functions of these peptides are largely unknown but they presumably mediate slow, modulatory synaptic actions in the dorsal horn neurons. The neuropeptides are always co-localized with other "classical" neurotransmitters.

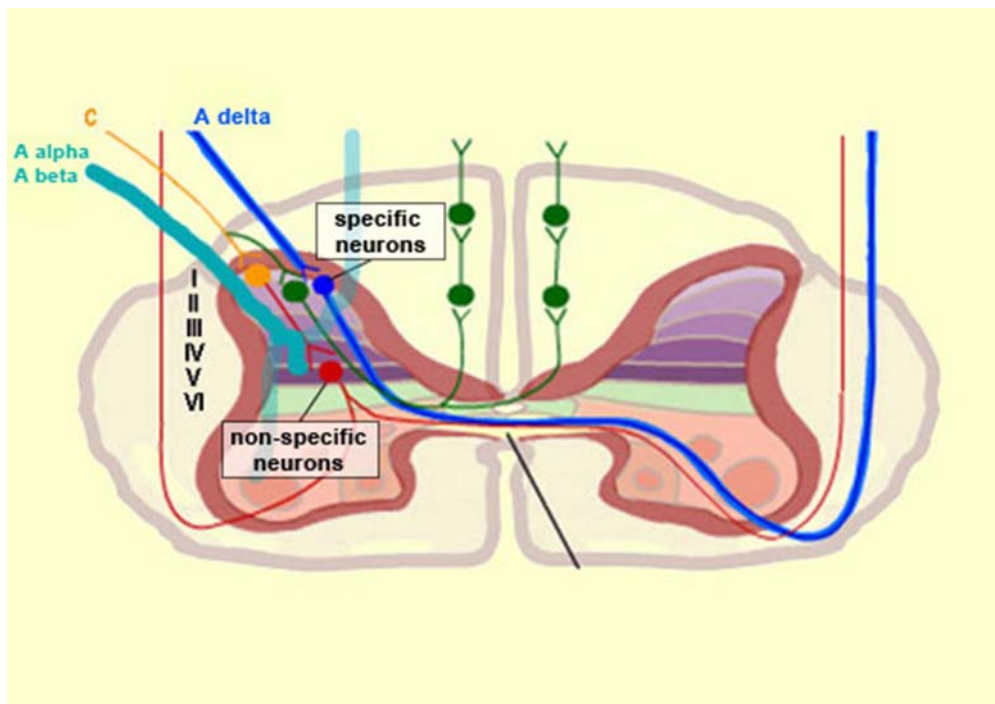


Figure 1.6 Four different nociceurons in the spinal cord.

There are four general types of nociceurons in the spinal cord (Figure 6.10):

1. High threshold mechanoreceptor neurons or nociceptive specific neurons. These neurons are excited only by noxious cutaneous and/or visceral stimuli. The nociceptive afferent fibers release glutamate and different neuropeptides to activate the dorsal horn neurons.
2. Chemical nociceptor neurons are excited by chemical or thermal noxious stimulus in the skin or in visceral organs.
3. Thermal nociceptor neurons are excited by chemical or thermal noxious stimulus in the skin or in visceral organs.
4. Polymodal-nociceptive neurons or multi, or wide dynamic range nociceptive neurons. These neurons are excited by both noxious and non-noxious cutaneous and/or visceral stimuli (polymodal nociceptive neurons). These neurons are activated by a variety of noxious stimuli (mechanical, thermal, chemical, etc.) and respond incrementally to increasing intensity of the stimuli.

Rexed lamina I contains a higher proportion of nociceptive specific neurons, whereas Rexed lamina II contains predominantly multi-receptive wide dynamic range neurons. The nociceptive-specific neurons alert the subject when a stimulus is noxious, and the multi-receptive neurons provide the subject with information about the parameters of the noxious stimulus. In general, C fibers release neuropeptides such as substance P whereas the A delta fibers release glutamate.

1.7. Classification of Pain

Pain has been classified into three major types:

1. ***Pricking pain.*** Pain caused by a needle, pin prick, skin cut, etc. - elicits a sharp, pricking quality, stinging pain sensation carried fast by the A delta fibers. The pain is precisely localized and of short duration. Pricking pain is also called fast pain, first pain or sensory pain. Pricking pain is present in all individuals and is a useful and necessary component of our sensory repertoire. Without this type of protective pain sensation, everyday life would be difficult. Pricking pain arises mainly from the skin, and carried mainly by A delta fibers which permits discrimination (i.e., permits the subject to localize the pain).

2. ***Burning pain or soreness pain.*** Pain caused by inflammation, burned skin, etc., is carried by the C fibers (slowly conducted pain nerve fibers). This type of pain is a more diffuse, slower to onset, and longer in duration. It is an annoying pain and intolerable pain, which is not distinctly localized. Like pricking pain, burning pain arises mainly from the skin. It is carried by the paleospinothalamic tract. (The old primitive transmission system for diffuse pain which does not permit exact localization.)

3. ***Aching pain*** is a sore pain. This pain arises mainly from the viscera and somatic deep structures. Aching pain is not distinctly localized and is an

annoying and intolerable pain. Aching pain is carried by the C fibers from the deep structures to the spinal cord.

2. Pain Tracts and Sources

Before considering the higher mechanisms involved in the perception of pain we will briefly examine the ascending pathways that carry nociceptive information from the spinal cord to higher brain centers. The anterolateral system, which is composed of a bundle of fibers, located in the ventrolateral aspect of the spinal cord, has long been recognized as conveying nociceptive and thermal information to higher brain centers. The cell bodies of the second order neurons that give rise to the anterolateral system are found primarily in lamina I, outer layers of lamina II and in laminae IV and V of the dorsal horn. These ascending second order projection neurons send axons and axon collaterals that decussate and terminate in the brainstem and thalamus. As described in chapter 7, studies of antidromically identified lamina I projection neurons have revealed these cells to have the properties of WDR (wide dynamic range), NS (nociceptive specific) and HPC (noxious heat, pinch and noxious cold) cells. In addition to the lamina I projection neurons with nociceptive properties, there are also a group of lamina I neurons sensitive to innocuous thermal stimuli and a group of lamina I neurons subserving the sense of itch.

The ascending pathways that mediate pain consist of three different tracts: the neospinothalamic tract, the paleospinothalamic tract and the archispinothalamic tract. The first-order neurons are located in the dorsal root ganglion (DRG) for all three pathways. Each pain tract originates in different spinal cord regions and ascends to terminate in different areas in the CNS.

2.1. Pain pathway

Neospinothalamic Tract

The neospinothalamic tract has few synapses and constitutes the classical lateral spinothalamic tract (LST) (Figure 2.1). The first-order nociceptive neurons (in the DRG) make synaptic connections in Rexed layer I neurons (marginal zone). Axons from layer I neurons decussate in the anterior white commissure, at approximately the

same level they enter the cord, and ascend in the contralateral anterolateral quadrant. Most of the pain fibers from the lower extremity and the body below the neck terminate in the ventroposterolateral (VPL) nucleus and ventroposteroinferior (VPI) nucleus of the thalamus, which serves as a relay station that sends the signals to the primary cortex. The VPL is thought to mainly be concerned with discriminatory functions. The VPL sends axons to the primary somatosensory cortex (SCI).

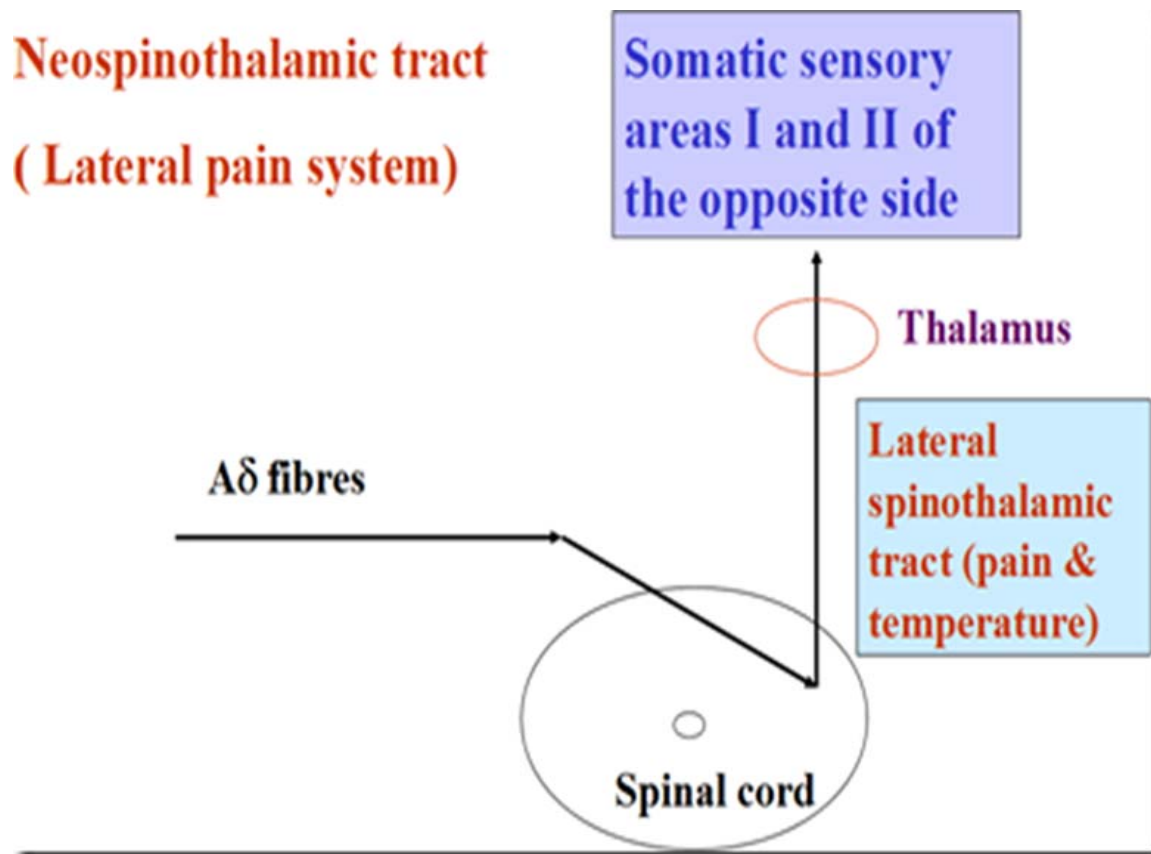


Figure 2.1
The neospinothalamic pathways.

The first-order nociceptive neurons from the head, face and intraoral structures have somata in the trigeminal ganglion (Figure 2.2). Trigeminal fibers enter the pons, descend to the medulla and make synaptic connections in the spinal trigeminal nucleus, cross the midline and ascend as trigeminothalamic tract (or trigeminal lemniscus, Figure 7.2). The A delta fibers terminate in the ventroposteromedial (VPM) thalamus, and the

C fibers terminate in the parafasciculus (PF) and centromedian (CM) thalamus (PF-CM complex). The PF-CM complex is located within the intralaminar thalamus and are known also as intralaminar (IL) nuclei. All of the neospinothalamic fibers terminating in VPL and VPM are somatotopically oriented and from there send axons that synapse on the

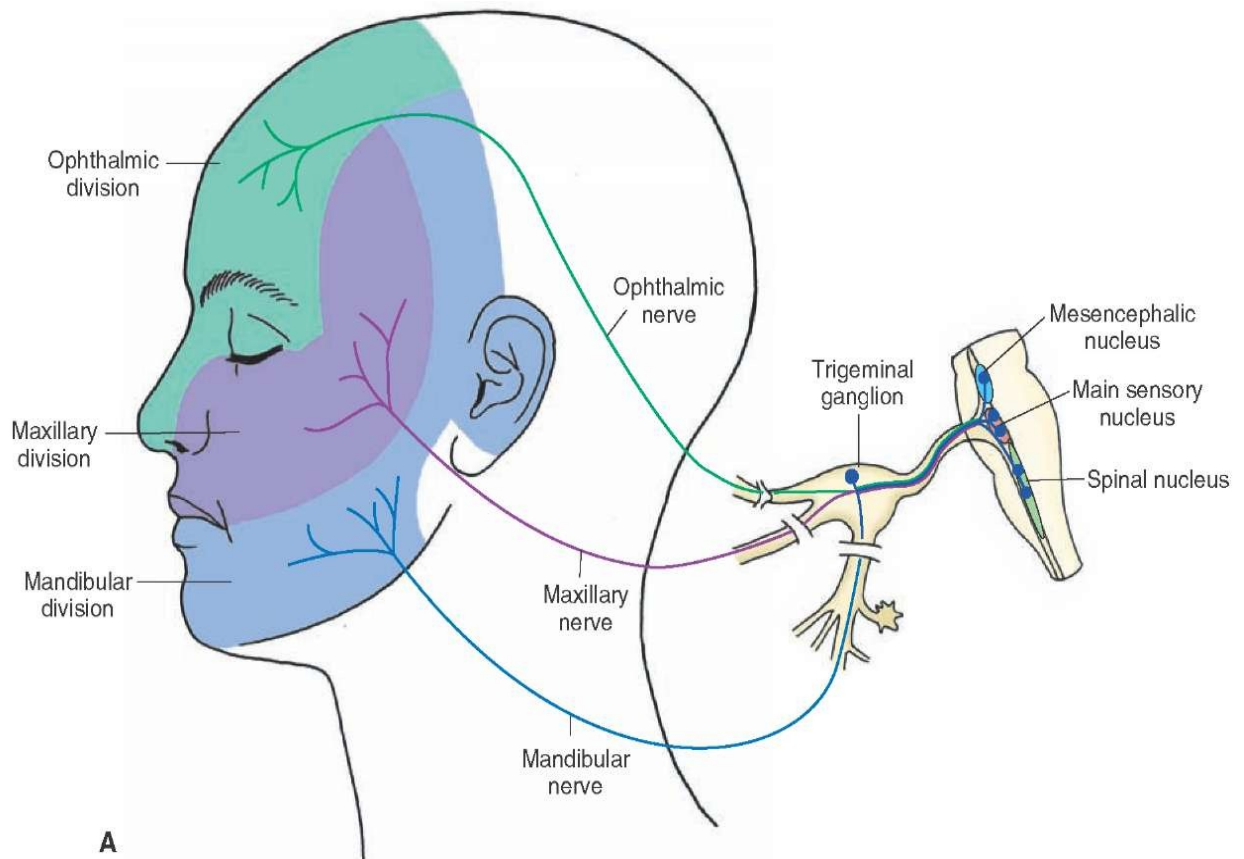


Figure 2.2

The sensory and spinal trigeminal tracts. The solid blue line represents the spinothalamic tract. The interrupted blue line represents the spinal trigeminal tract. The purple line represents the sensory trigeminal tract

primary somatosensory cortex (SC I - Brodman areas 1 & 2). This pathway is responsible for the immediate awareness of a painful sensation and for awareness of the exact location of the painful stimulus.

Paleospinothalamic Pathway

The paleospinothalamic tract is phylogenetically old. The majority of the first-order nociceptive neurons make synaptic connections in Rexed layer II (substantia gelatinosa) and the second-order neurons make synaptic connections in laminae IV-VIII. The second-order neurons also receive input from mechanoreceptors and thermoreceptors. The nerve cells that furnish the paleospinothalamic tract are multireceptive or wide dynamic range nociceptors. Most of their axons cross and ascend in the spinal cord primarily in the anterior region and thus called the anterior spinal thalamic tract (AST). These fibers contain several tracts. Each of them makes a synaptic connection in different locations: 1) in the mesencephalic reticular formation (MFR) and in the periaqueductal gray (PAG), and they are also called spinoreticular tract; 2) in the tectum, and these fibers are known as the spinotectal or spinomedullary tract; 3) in the PF-CM complex (IL) and they are known as the spinothalamic tract (Figure 2.3). The above three fiber tracts are known also as the paleospinothalamic tract. The innervation of these three tracts is bilateral because some of the ascending fibers do not cross to the opposite side of the cord. From the PF and CM complex, these fibers synapse bilaterally in the somatosensory cortex (SC II-Brodman area 3). The paleospinothalamic pathway also activates brain stem nuclei which are the origin of descending pain suppression pathway regulating noxious input at the spinal cord level (see next chapter).

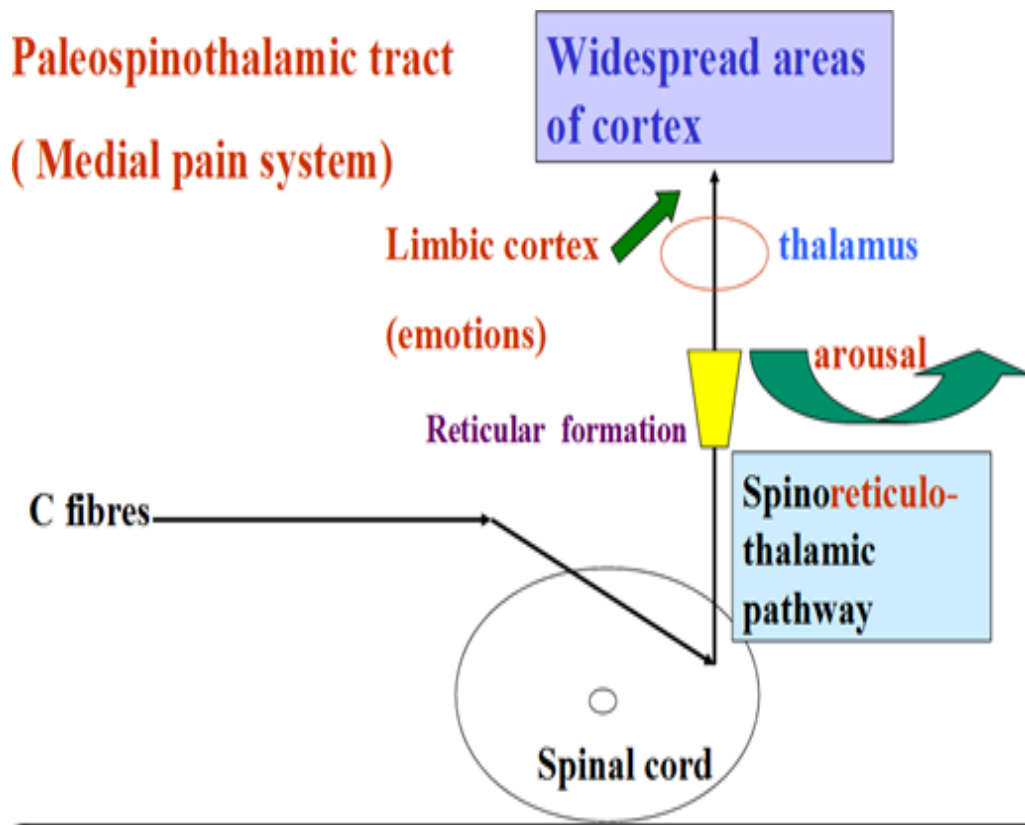


Figure 2.3
The paleospinothalamic pathway.

The multisynaptic tracts which course via the reticular formation also project to the PF-CM (IL) complex. There are extensive connections between the IL and the limbic areas such as the cingulate gyrus and the insular cortex, which is thought to be involved in processing the emotional components of pain. That is to say, the insular cortex integrates the sensory input with the cortical cognitive components to elicit the response to the sensation. The limbic structures, in turn, project to the hypothalamus and initiate visceral responses to pain. The intralaminar nuclei also projects to the frontal cortex, which in turn projects to the limbic structures where the emotional response to pain is mediated.

Archispinothalamic Pathway

The archispinothalamic tract is a multisynaptic diffuse tract or pathway and is phylogenetically the oldest tract that carries noxious information. The first-order

nociceptive neurons make synaptic connections in Rexed layer II (substantia gelatinosa) and ascend to laminae IV to VII. From lamina IV to VII, fibers ascend and descend in the spinal cord via the multisynaptic propriospinal pathway surrounding the grey matter to synapse with cells in the MRF-PAG area. Further multisynaptic diffuse pathways ascend to the intralaminar (IL) areas of the thalamus (i.e., PF-CM complex) and also send collaterals to the hypothalamus and to the limbic system nuclei. These fibers mediate visceral, emotional and autonomic reactions to pain.

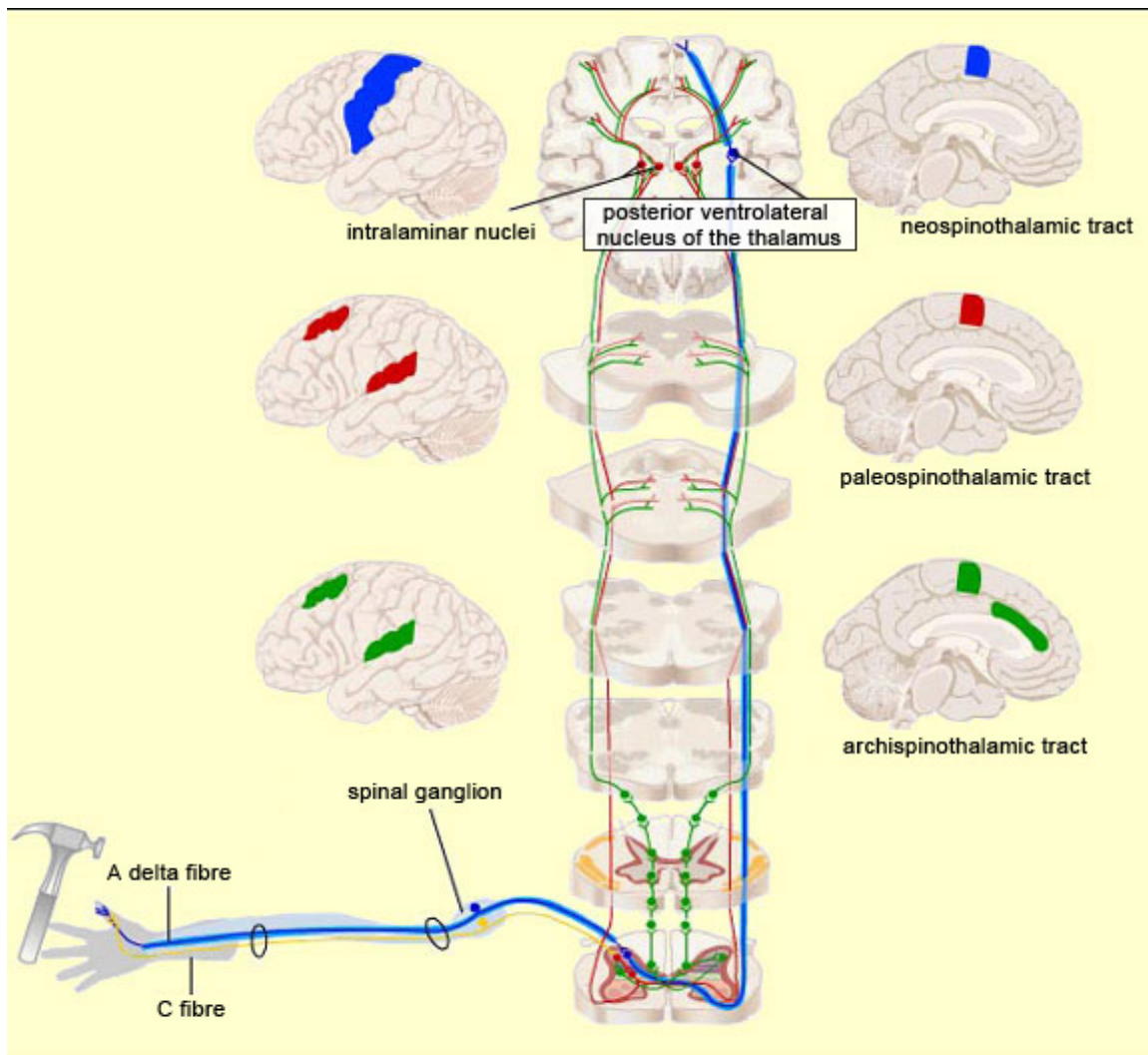


Figure 2.4

Summary of the three pathways carrying pain sensation.

Figure 2.4 summarizes the three major spinal thalamic pathways. Information about bodily events is conveyed by primary sensory fibers to higher brain centers

through the dorsal column medial lemniscal pathways. This route is considered a "touch pathway," separate from the spinal thalamic pathways. However, recent reports indicate that the dorsal column can also carry noxious information from the viscera and widespread skin regions.

2.2 Sources of Pain

Somatic Pain

Somatic pain can be classified as either:

- 1) cutaneous, superficial or peripheral pain and
- 2) deep pain.

Cutaneous, Superficial or Peripheral Pain. Pain that arises from the skin and muscles or peripheral nerves themselves. In general, this pain has two components, the initial response (a) followed by later response (b). These signals are transmitted via different pathway.

Pricking pain reaches the CNS via neospinothalamic tract (i.e., LST) to the VPL (or VPM) and to the SCI.

Burning and soreness pain resulting from tissue damage reaches the CNS via the paleospinothalamic tract (AST) and archispinothalamic tract to brain stem nuclei and to PF-CM complex, etc.

Deep pain. This pain arises from joint receptors tendons and fascia (i.e., deep structures). The quality of deep pain is dull, aching or burning. Deep pain is accompanied by a definite autonomic response associated with sweating and nausea, changes in blood pressure and heart rate. Somatic deep pain reaches the CNS mainly via the paleospinothalamic and archispinothalamic tract (Figure 2.4).

Reaction to Somatic Pain. Sudden, unexpected damage to the skin is followed by three responses:

Startle response. This is a complex psychosomatic response to a sudden unexpected stimulus which includes: A flexion reflex, postural readjustment and orientation of the head and eyes to examine the damaged area.

Autonomic response. This response includes: NE and E release, ACTH and/or cortisol release, and vasoconstriction and piloerection.

Behavioral response. This response includes: Vocalization, rubbing designed to diminish pain, learning to respond to sudden pain and psychosomatic pain.

Visceral Pain

In the visceral organs, nociceptors respond to mechanical stimulation such as pressure, tissue damage, and chemical stimulation.

Most noxious information carried by visceral afferents does not give rise to conscious sensation. Visceral pain is diffuse, less precisely graded and typically accompanied by slowing of the heart, lowered blood pressure, cold sweats and nausea. It conveys also hunger, thirst, electrolyte balance, irregularity in the respiratory and circulatory systems. Many of these signals reach the CNS bilaterally (Figure 7.6) by the following three channels:

In the visceral organs, free nerve endings are scattered, and any stimulus that excites these nerve endings causes visceral pain. Such stimuli include spasm of the smooth muscle in a hollow viscus, or distention or stretching of the ligament, such as a stone blocking the ureter or the gall ducts. Stretching of the tissues such as intestinal obstruction can also provoke visceral pain. Visceral pain is also caused by chemical means as a result of gastrointestinal lesions, and tumors as well as thrombosis of an artery. In many cases, visceral pain is not localized to the site of its cause, rather in a distant site.

Thalamic Pain

Stroke or occlusion in the thalamogeniculate artery (a branch of the posterior cerebral artery), which supplies the lateroposterior half of the thalamus, can result in a thalamic lesion, which is often accompanied by neurologic conditions several months after the initial event. The condition is associated with a devastating intracranial pain in the contralateral side of the thalamic lesion and sensory loss. In some cases, severe

facial pain is experienced without any sensory loss. The pain resulting from an intracranial lesion is also termed "central pain."

Lesions in the spinothalamic tract and its targets of termination as well as local manifestations of diencephalic lesions are usually complex. They can induce alteration of sensory, motor and endocrine components because of the functional diversity of the thalamus. Subjects with this syndrome experience spontaneous aching and burning pain in body regions where sensory stimuli normally do not lead to pain. Because the brain and the spinal cord do not contain nociceptors, the pathological process presumably directly stimulates nociceptive pathways, or it prevents the activation of the pain suppression pathways. This condition is known also as thalamic pain syndrome or Dejerive-Roussy syndrome.

Neuropathic Pain

Neuropathic pain is a sharp, shooting and devastating pain. It is a persistent pain that arises from functional changes occurring in the CNS secondary to peripheral nerve injury. Once the nerve is damaged, the damaged nerve elicits sustained activation of nociceptors and/or nociceptive afferents. The neuropathic pain is due to an abnormal activation of the nociceptive system without specifically stimulating the nociceptors. Neuroplastic changes occurring in the CNS secondary to the afferent barrage are believed to culminate in CNS neuronal hyperexcitability. Many scientists suggest that "sensitization" of the nervous system following injury is a factor in neuropathic pain. Neuropathic pain can usually be controlled by anti-inflammatory drugs and opioids. In some cases, such as in diabetics, AIDS, cancer, etc., no treatment or relief is available to neuropathic pain. Neuropathic pain should not be confused with neurogenic pain, a term used to describe pain resulting from injury to a peripheral nerve but without necessarily implying any neuropathy.

Psychosomatic Pain

Psychic reaction to pain includes all the well-known responses to pain such as anguish, anxiety, crying, depression, nausea and excess muscular excitability through

the body. These reactions vary tremendously from one person to another following a comparable degree of pain stimuli. The sensation of pain can be influenced by emotions, past experiences and suggestions. The same stimulus can elicit different responses in different subjects under the same conditions.

Recently, Positron Emission Tomography (PET) has been used to study pain pathways and psychosomatic pain centers. For example, volunteers had their hands dipped in hot water (50° C) while they were conscious. They then dipped their hand again in hot water (50° C) after a post-hypnotic suggestion that the pain would be either more or less unpleasant than the first time. The PET scans of their brains showed that activity in the anterior cingulate cortex changed in accordance with how unpleasant they expected the pain to be. However, the intensity in the primary somatosensory cortex remained constant (i.e., the emotional component of pain is independent of its sensation).

Referred Pain

Referred pain is a painful sensation at a site other than the injured one. The pain is not localized to the site of its cause (visceral organ) but instead is localized to a distant site. One possible exception is that the axons carry pain information from the viscera enter into the spinal cord by the same route as the cutaneous pain sensation axons. Within the spinal cord there is a convergence of the information on the same nociceurons. This convergence gives rise to the phenomenon of referred pain. For example, pain associated with angina pectoris, or myocardial infarction is referred to the left chest, left shoulder, and upper left arm (Figure 2.5). Pain resulting from distention of the colon is referred to the periumbilical area

Cardiac pain is referred to the left hand. The left hand and the heart are developed from the same myotome and innervated by the same nerve.

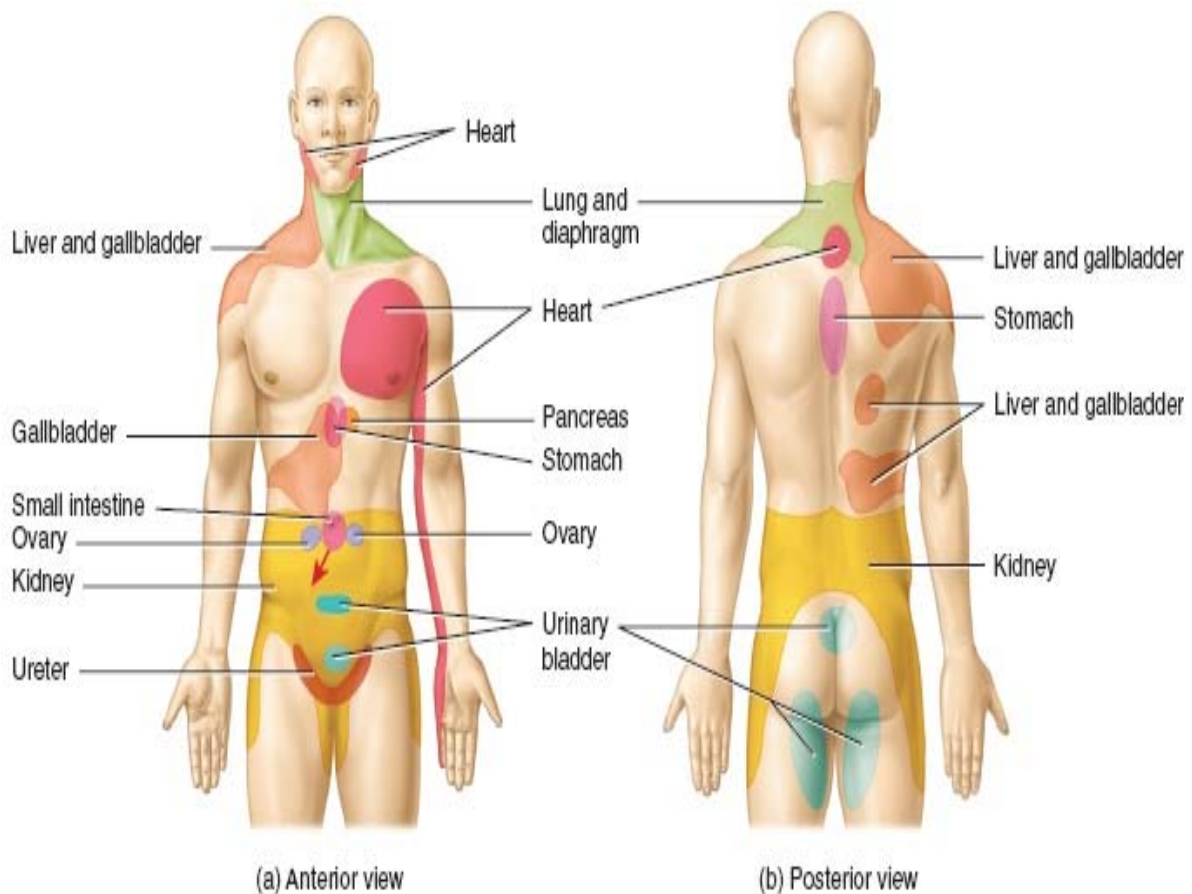
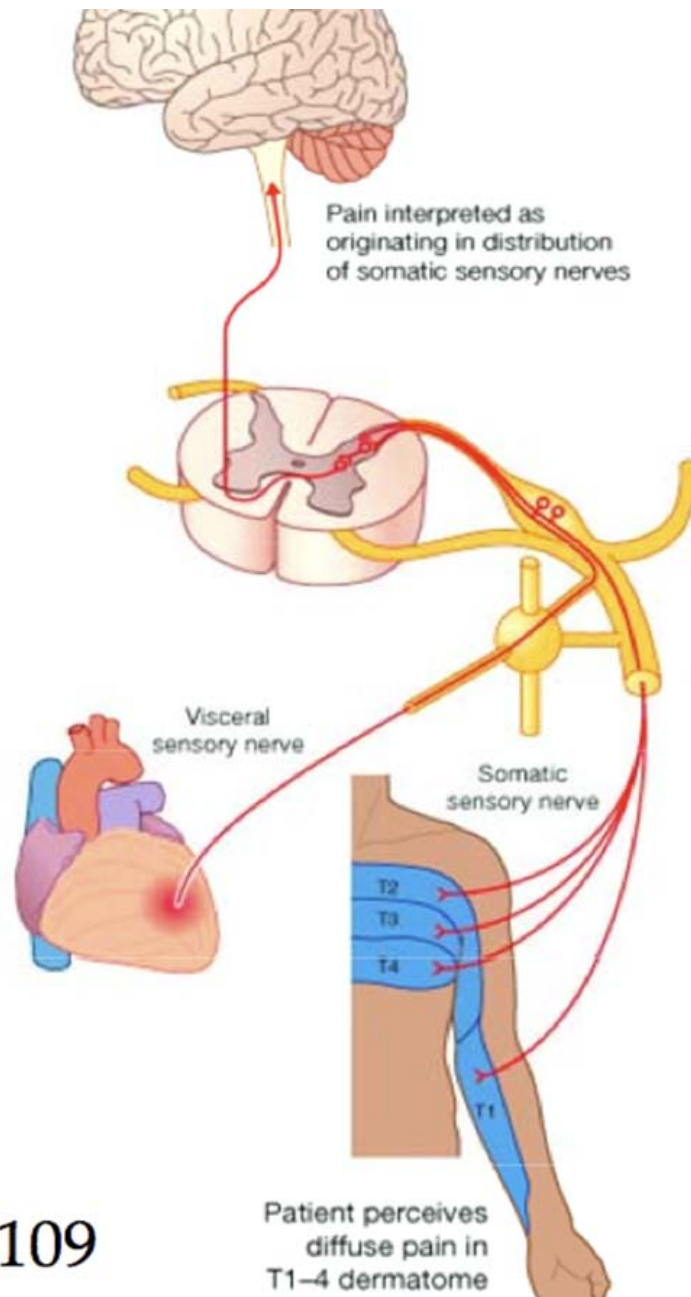


Figure 2.5

Area of referred pain (i.e., pain originating from the gall bladder is referred to the right chest and back).

The following are some hypothesis to explain referred pain

1. Common dermatome hypothesis. When pain is referred, it is usually to a structure that developed from the same embryonic segment or dermatome as the structure in which the pain originates. Radiating pain down the left arm is the result of a myocardial infarction (Figure 2.6), or pain originating from the shoulder (dermatomes 3-5).
2. Convergence and facilitation theories (Figure 2.7). Inputs from visceral and skin receptors converge on the same spinal cord neuron (i.e., viscerosomatic neurons). Therefore, visceral pain is referred to skin area because the nociceptors' terminals from the viscera terminate in the spinal cord on the same neurons that receive input from the skin.



3.109

Figure 2.6

Convergence in referred pain is carried via the paleospinothalamic tract.

3. Facilitation or irritable focus. Pain impulses from the viscera alone are unable to pass directly from spinal cord neurons to the brain, but create an "irritable focus". When visceral and skin impulses arrive together, the information transmitted to

higher centers and the brain interprets the pain as being from the skin (Figure 2.7).

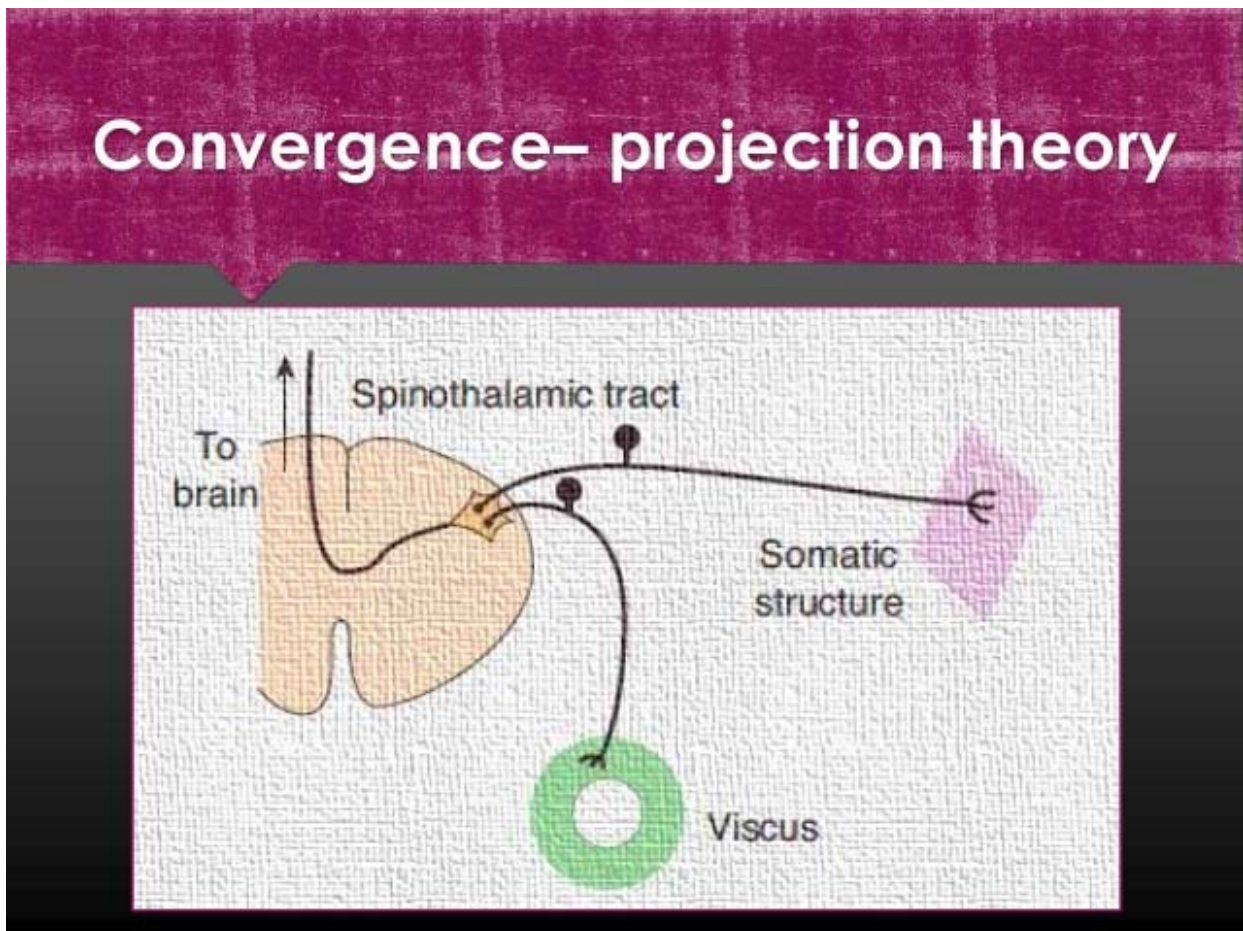


Figure 2.7
Convergence of referred pain.

Learned phenomenon. Visceral information arrives in the CNS. However, the brain interprets that the impulses originate from the site of a previous surgical operation, trauma or localized pathologic process.

Phantom (illusory) Pain

Phantom or illusory pain is the experience of pain without any signals from nociceptors. It occurs in a subject with previous injuries such as amputation in which the dorsal roots are literally absent from the cord. Even though no sensory signals can

enter the cord, the subject often feels extreme pain in the denervated parts of the body. For example, an amputee will often apparently feel pain in a part of his body that has been removed. The phenomenon of phantom limb pain is a common experience after a limb has been amputated or its sensory roots have been destroyed in which the pain is felt in a part of the body that no longer exists. Pain from an amputated arm is referred to the viscera as a result of disruption to the “balance” between different peripheral inputs to the dorsal horn. A complete break of the spinal cord also often leads to a phantom body pain below the level of the break. The source of phantom pain is complex and not well understood. It has been suggested that there may be abnormal discharges 1) from the remaining cut ends of nerves which grow into nodules called neuromas, 2) from overactive spinal neurons, 3) from abnormal flow of signals through the somatosensory cortex, or 4) from burst-firing neurons in the thalamus.

2.3 Acute Pain

Acute pain arises from activation of nociceptors for a limited time and is not associated with significant tissue damage (e.g., a pin prick).

2.4 Chronic Pain

Chronic pain is prolonged pain lasting for months or longer that arises from tissue injury, inflammation, nerve damage, tumor growth, lesion or occlusion of blood vessels. Chronic or inflammatory pain can sensitize (see "Sensitization" below) the nervous system, evoking chemical, functional, and even structural changes that serve to “prime the pain-processing pump”. Chronic pain, such as lower back pain, rheumatoid and osteoarthritis, and headache (see "Headaches" below) may result from constant inflammatory activity which activates G proteins. In some cases, the pain persists long after the injury heals, but there is no treatment that will eliminate the pain.

Sensitization

One possible explanation for chronic pain is a phenomenon called sensitization. Following continuation and prolong noxious stimulation, nearby silent nociceptive

neurons that previously were unresponsive to stimulation, now become responsive. In addition, some of the chemicals produced and released at the injured site also alter the physiological properties of nociceptors. The nociceptors begin to initiate pain signals spontaneously, which cause chronic pain. In addition, weak stimuli, such as a light touch that previously had no effect on these nociceptors, will further activate the nociceptors which result in severe pain signals. This phenomenon is referred to as “peripheral sensitization.” The outcome of peripheral sensitization results in a greater and more persistent barrage of nerve impulses firing in the CNS. The persistent barrage of nerve impulses results in long-term changes in nerve cell activity at the level of the spinal cord and higher centers in the brain. This phenomena is referred to as “central sensitization”. It appears that peripheral and central sensitization persists after the injury apparently has healed. The sensitization of nociceptive neurons after injury results from the release of different chemicals from the damaged area. It is known that substance P and calcitonin gene-related peptides are released from peripheral nerve ending which stimulate most cells to release algescic substances which further potentiates the pain from the injury. In contrast, central sensitization resulting from severe and persistent injury which cause prolonged release of glutamate on nociceptive dorsal horn cells, this constant glutamate release via G protein dependant phosphorylation cascades results in opening of postsynaptic ion channels gated by the NMDA receptors. This phenomenon is also termed "wind up." This activation produces hyperexcitability of the dorsal horn cells and causes "central sensitization." Pain experts now agree that treating chronic pain early and aggressively yields the best results and prevents patients from developing physical and psychological conditions that could worsen the pain.

Fibromyalgia

Fibromyalgia is characterized by widespread chronic pain throughout the body, including fatigue, anxiety and depression. It is now believed that it has a genetic component which tends to run in families.

Headaches

A headache is a poorly understood type of pain that can be either acute or chronic. There are about 300 different types and causes of headaches. The following are some categories of disorders associated with headaches:

Intracranial structural disease

Infectious disease

Cerebrovascular ischemia

Cerebral vein thrombosis

Metabolic disease

Toxic exposures

Medications

Extracranial pressure disorders

Sinusitis

Vasculitis and collagen vascular disease

Hemorrhage (parenchymal and subarachnoid)

Trauma

Withdrawal syndromes

Severe hypertension

Dental, cranial vault, TMJ, and myofascial disorders

Cervical spine and occipitocervical junction disorders

2.5 Summary

Because of the importance of warning signals of dangerous circumstances, several nociception pathways are involved to transmitting these signals and some of them are redundant.

The neospinothalamic tract conducts fast pain (via A delta fibers) and provides information of the exact location of the noxious stimulus, and the multisynaptic

paleospinothalamic and archispinothalamic tracts conduct slow pain (via C fibers), a pain which is poorly localized in nature. (Figure 2.4)

Pain activates many brain areas, which link sensation, perception, emotion, memory and motor reaction. Therefore, many pain clinics target their treatments to block the perception of pain using psychosomatic means of treatments such as biofeedback, hypnosis, physical therapy, electrical stimulation, and acupuncture-multimodal treatment.

3. Pain Modulation and Mechanisms

3.1 Pain Modulation

Most, if not all, ailments of the body cause pain. Pain is interpreted and perceived in the brain. Pain is modulated by two primary types of drugs that work on the brain: analgesics and anesthetics. The term analgesic refers to a drug that relieves pain without loss of consciousness. The term central anesthesia refers to a drug that depresses the CNS. It is characterized by the absence of all perception of sensory modalities, including loss of consciousness without loss of vital functions.

Opiate Analgesia (OA)

The most effective clinically used drugs for producing temporary analgesia and relief from pain are the opioid family, which includes morphine, and heroin. There are currently no other effective pain therapeutic alternatives to opiates. Several side effects resulting from opiate use include tolerance and drug dependence (addiction). In general, these drugs modulate the incoming pain information in the spinal and central sites, as well as relieve pain temporarily, and are also known as opiate producing analgesia (OA). Opiate antagonist is a drug that antagonizes the opioid effects, such as naloxone or maltroxone, etc. They are competitive antagonists of opiate receptors. The brain has a neuronal circuit and endogenous substances to modulate pain.

Endogenous Opioids

Much of what we know about the central mechanisms of pain control comes from experiments in which electrical and pharmacological stimuli were applied to certain areas of rat and human brains.

When an electrode is implanted in and used to apply an electrical stimulus to the periaqueductal grey matter of a rat's brain, the initial effect, as determined from the rat's behaviour, is analgesic. This electrical stimulus may also reduce the activity that a nociceptive stimulus normally generates in the neurons of the dorsal horn of the spinal

cord. But this same stimulus has no effect on the rat's sense of touch or sensitivity to temperature.

Neurosurgeons have successfully relieved severe pain in human patients by means of electrodes implanted close to the periaqueductal grey matter in their brains. This technique, known as deep brain stimulation (DBS), has been used since the 1980s to treat recalcitrant pain.

Researchers suspected very early on that this electrical stimulation might produce this analgesia by causing the release of endorphins, in part because administering naloxone, an opiate antagonist, blocked this analgesic effect.

More direct evidence was obtained when local microinjections of morphine into the periaqueductal grey matter were found to produce a strong analgesic effect. This microinjection method enabled researchers to identify several areas of the medulla oblongata that are involved in suppressing pain, such as the nucleus raphe magnus, the gigantocellular nucleus, and the lateral reticular nucleus of the solitary tract. But depending on which part of the periaqueductal grey matter received the electrical stimulus, naloxone did not always block the analgesia, which indicated that the descending pain-control pathways utilize several other neurotransmitters besides opioids. For example, neuroscientists now have extensive knowledge of the serotonergic pathways descending from the raphe nuclei and have learned that serotonin antagonists can also cancel out the analgesic effect produced by electrical stimulation of the brain.

Opioidergic neurotransmission is found throughout the brain and spinal cord and appears to influence many CNS functions, including nociception, cardiovascular functions, thermoregulation, respiration, neuroendocrine functions, neuroimmune functions, food intake, sexual activity, aggressive locomotor behavior as well as learning and memory. Opioids exert marked effects on mood and motivation and produce euphoria.

Three classes of opioid receptors have been identified: μ -mu, δ -delta and κ -kappa. All three classes are widely distributed in the brain. The genes encoding each one of them have been cloned and found to be members of the G protein receptors. Moreover,

three major classes of endogenous opioid peptides that interact with the above opiate receptors have been recognized in the CNS: β -endorphins, enkephalins and the dynorphins. These three opioid peptides are derived from a large protein precursor by three different genes: the proopiomelanocortin (POMC) gene, the proenkephalin gene and the prodynorphin gene. The opioid peptides modulate nociceptive input in two ways: 1) block neurotransmitter release by inhibiting Ca^{2+} influx into the presynaptic terminal, or 2) open potassium channels, which hyperpolarizes neurons and inhibits spike activity. They act on various receptors in the brain and spinal cord. Enkephalins are considered the putative ligands for the δ receptors, β endorphins for the μ -receptors, and dynorphins for the κ receptors. The various types of opioid receptors are distributed differently within the central and peripheral nervous system. There is evidence for functional differences in these receptors in various structures. This explains why many unwanted side effects occur following opiate treatments. For example, mu (μ) receptors are widespread in the brain stem parabrachial nuclei, a respiratory center and inhibition of these neurons elicits respiratory depression.

Central or peripheral terminals of nociceptive afferent fibers contain opiate receptors where exogenous and endogenous opioids could act to modulate the ability to transmit nociceptive information. Moreover, high densities of opiate receptors are found in periaqueductal gray (PAG), nucleus raphe magnus (NRM), and dorsal raphe (DR) in the rostral ventral medulla, in the spinal cord, caudate nucleus (CN), septal nucleus, hypothalamus, habenula and hippocampus. Additional detail on opiate receptors is provided later in this lecture.

Systemically administered opioids at analgesic doses activate spinal and supraspinal mechanisms via μ , δ , and κ type opioid receptors and modulate pain signals.

3.2 Neuronal Circuits that Modulate Pain

For many years it was suggested that somewhere in the CNS there is a circuit that can modulate incoming pain information. The gate control theory and the ascending/descending pain transmission system are two suggestions of such a circuit.

Gate Control theory

The first pain modulatory mechanism called the "Gate Control" theory was proposed by Melzack and Wall in the mid 1960s. The concept of the gate control theory is that non-painful input closes the gates to painful input, which results in prevention of the pain sensation from traveling to the CNS (i.e., non-noxious input [stimulation] suppresses pain).

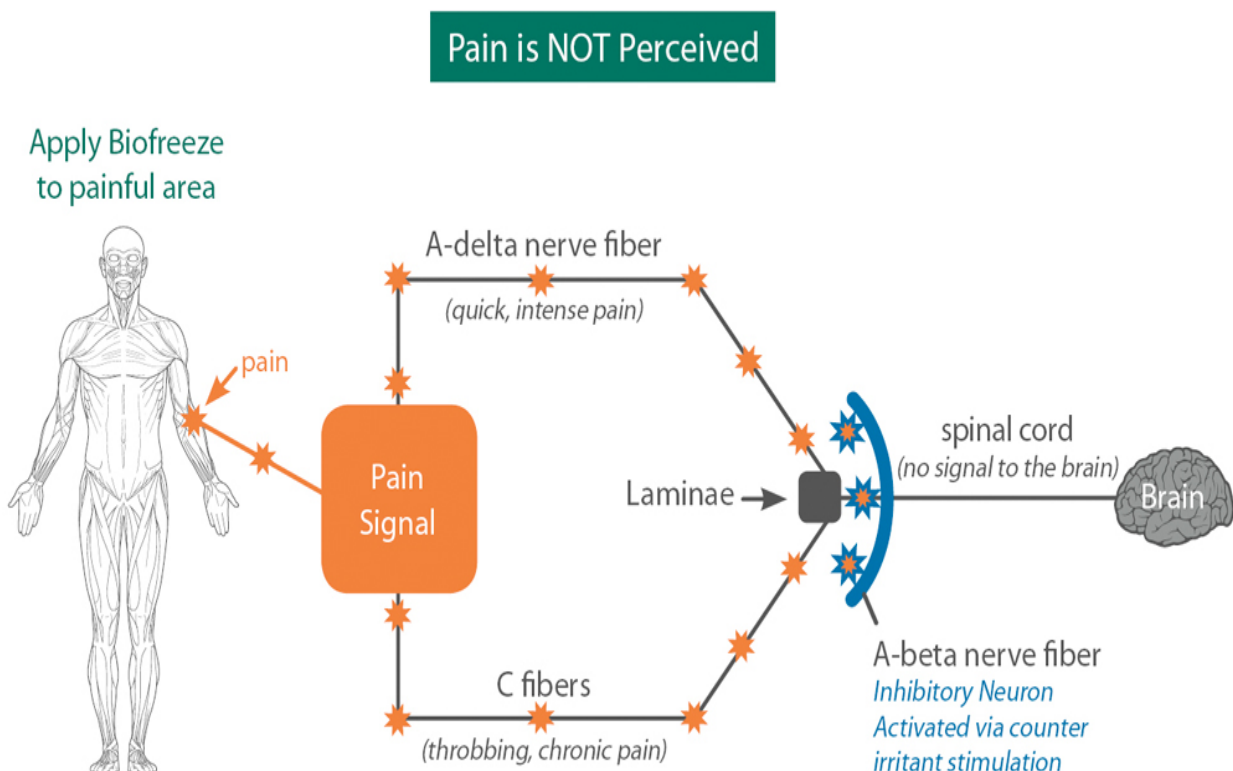


Figure 3.1

The gate control theory of pain modulation. The gate control theory is based on presynaptic inhibition of pain information produced by mechanical stimulation, and provides the basic rationale for the TENS.

The theory suggests that collaterals of the large sensory fibers carrying cutaneous sensory input activate inhibitory interneurons, which inhibit (modulate) pain transmission information carried by the pain fibers. Non-noxious input suppresses pain, or sensory input "closes the gate" to noxious input (Figure 3.1). The gate theory predicts

that at the spinal cord level, non-noxious stimulation will produce presynaptic inhibition on dorsal root nociceptor fibers that synapse on nociceptors spinal neurons (T), and this presynaptic inhibition will block incoming noxious information from reaching the CNS (i.e., will close the gate to incoming noxious information).

The gate theory was the rationale for the idea behind the production and the use of transcutaneous electrical nerve stimulation (TENS) for pain relief. To be effective, the TENS unit produces two different current frequencies below the pain threshold that can be tolerated by the patient. This procedure has partial success in pain therapy.

Stimulation produced analgesia (SPA)

Evidence for an intrinsic analgesia system was demonstrated by intracranial electrical stimulation of certain discrete brain sites. These areas are the periaqueductal gray (PAG) and nucleus raphe magnus (NRM), dorsal raphe (DR), caudate nucleus (CN), septal nucleus (Spt) and other nuclei. Such stimulation inhibits pain, (i.e., producing analgesia without behavioral suppression), while the touch, pressure and temperature sensation remain intact. SPA is more pronounced and lasts a longer time after stimulation in humans than in experimental animals. Moreover, during SPA, the subjects still respond to nonpainful stimuli such as touch and temperature within the circumscribed area of analgesia. The most effective CNS sites for SPA are the PAG and the raphe nuclei (RN).

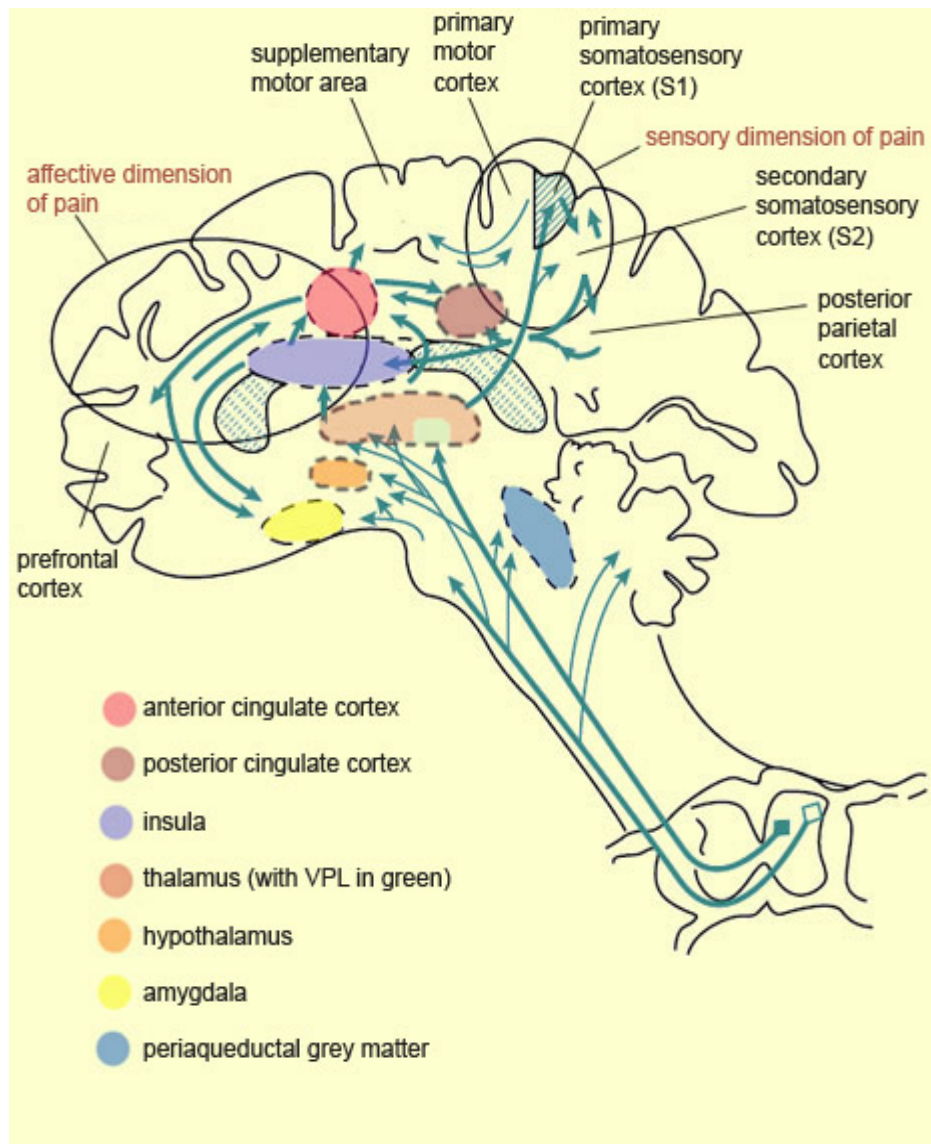


Figure 3.2

Periaqueductal gray and raphe nucleus stimulation produces analgesia.

Electrical stimulation of PAG or NRM inhibits spinal thalamic cells, (i.e. spinal neurons that project monosynaptically to the thalamus) in laminae I, II and V so that the noxious information from the nociceptors are modulated at the spinal cord level. PAG has neuronal connections to NRM.

The action of the PAG most likely occurs by activation of the descending pathway from NRM and probably also by activation of ascending connections acting on higher subcortical levels of the CNS. Moreover, electrical stimulation of PAG or NRM produces behavioral analgesia, (i.e., stimulation produced analgesia, see (Figure 3.2).

Stimulation produced analgesia (SPA) elicits release of endorphin and is blocked by the opiate antagonist naloxone.

During PAG and/or RN stimulation, serotonin (5-HT) is also released from ascending and descending axons in subcortical nuclei, in spinal trigeminal nuclei and in the spinal cord. This release of 5-HT modulates pain transmission by inhibiting incoming sensory activity. Depletion of 5-HT by electrical lesion of the raphe nuclei or by a neurotoxic lesion produced by local injection of a chemical agent like parachlorophenylalanine (PCPA) results in blocking the ability of both opiate (intracranial and systemic) and electrical stimulation to produce analgesia.

Stimulation Produced Analgesia (SPA) (continued)

To verify whether the electrical stimulation produced analgesia via the release of opiate and serotonin, the area was locally microinjected with morphine or 5-HT. These microinjections indeed produce analgesia (Figure 8.3). These procedures also provide a method of identifying brain regions associated with pain suppression and help to produce a map of pain centers. The most effective method of producing opiate analgesia (OA) is by intracerebral injection of morphine into the PAG.

The PAG and RN and other brain structures where analgesia is produced are also rich in opiate receptors. Intracerebral opioid administration produced analgesia and SPA can be blocked by either systemic or by local microinjections of naloxone, the morphine antagonist, into the PAG or RN. Therefore, it has been suggested that the two (OA and SPA) operate by a common mechanism.

If OA and SPA act through the same intrinsic system, then the hypothesis that opiates activate a pain-suppression mechanism is more likely. In fact, present evidence indicates that microinjections of an opiate into the PAG activate an efferent brainstem system that suppresses pain transmission at segmental (spinal cord) levels. These observations indicate that analgesia elicited from the PAG requires a descending pathway to the spinal cord.

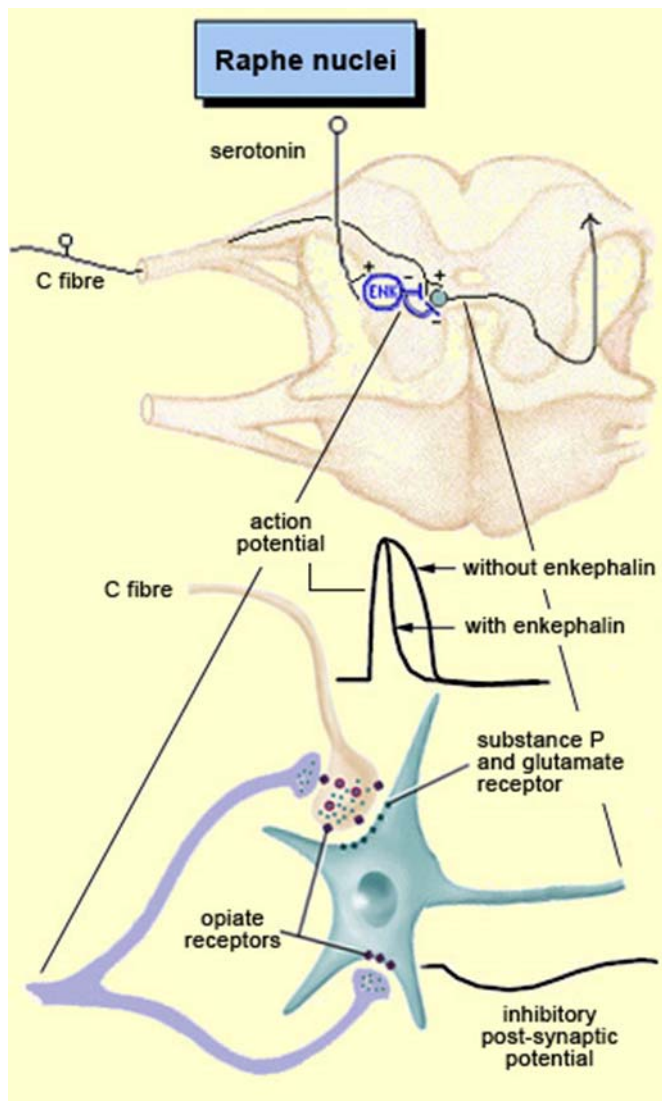


Figure 8.3

Periaqueductal gray and raphe nucleus electrical stimulation produces analgesia.

3.3 Pain Mechanisms

Ascending and Descending Pain Suppression Mechanism

The primary ascending pain fibers (the A δ and C fibers) reach the dorsal horn of the spinal cord from peripheral sites to innervate the nociceptor neurons in Rexed laminae I & II. Cells from Rexed lamina II make synaptic connections in Rexed layers IV to VII. Cells, especially in laminae I and VII of the dorsal horn, give rise to ascending spinothalamic tracts. At the spinal level, opiate receptors are located at the presynaptic ends of the nociceurons and at the interneural level layers IV to VII in the

dorsal horn. Activation of opiate receptors at the interneuronal level produces hyperpolarization of the neurons, which result in the inhibition of firing and the release of substance P, a neurotransmitter involved in pain transmission, thereby blocking pain transmission. The circuit that consists of the periaqueductal gray (PAG) matter in the upper brain stem, the locus coeruleus (LC), the nucleus raphe magnus (NRM) and the nucleus reticularis gigantocellularis (Rgc) contributes to the descending pain suppression pathway, which inhibits incoming pain information at the spinal cord level.

As mentioned previously, opioids interact with the opiate receptors at different CNS levels. These opiate receptors are the normal target sites for neurotransmitters and endogenous opiates such as the endorphins and enkephalins. As a result of binding at the receptor in subcortical sites, secondary changes which lead to a change in the electrophysiological properties of these neurons and modulation of the ascending pain information.

What activates the PAG to exert its effects? It was found that noxious stimulation excites neurons in the nucleus reticularis gigantocellularis (RGC). The nucleus Rgc innervates both the PAG and NRM. The PAG sends axons to NRM, and neurons in NRM send their axons to the spinal cord. Moreover, bilateral dorsolateral funiculus (DLF) lesions (DLFX) block the analgesia produced by both electrical stimulation and by microinjection of opiates directly into the PAG and NRM, but they only attenuate the systemic analgesic effects of opiates (Figure 8.4). These observations support the hypothesis that discrete descending pathways in the DLF are necessary for both OA and SPA.

The DLF is comprised of fibers originating from several brainstem nuclei, which are serotonergic (5-HT) from neurons located within the nucleus raphe magnus (NRM); dopaminergic neurons originating from ventral tegmental area (VTA) and adrenergic neurons originating from the locus coeruleus (LC). These descending fibers suppress noxious input at the nociceptive spinal cord neurons in laminae I, II, and V.

Opiate receptors have also been found in the dorsal horn of the spinal cord, mainly in Rexed laminae I, II, and V, and these spinal opiate receptors mediate inhibitory effects on dorsal horn neurons transmitting nociceptive information. The action of

morphine appears to be exerted both in the spinal cord and brainstem nuclei (i.e., PAG and NRM). Systemic morphine acts on both brain stem and spinal cord opiate receptors to produce analgesia. Morphine binds the brainstem opiate receptors, which activates the brainstem descending serotonergic pathway to spinal cord (i.e., the DLF), and they have an opioid-mediated synapse at the level of the spinal cord.

This observation suggests that noxious stimuli (rather than non-noxious stimulus - see Gate Theory) are critical for activation of the descending pain modulation circuit (i.e., pain suppresses pain via the descending DLF pathway).

In addition, there are ascending connections from the PAG and raphe nuclei to PF-CM complex. These thalamic areas are part of the ascending pain modulation at the diencephalon level.

Stress-Induced Analgesia (SIA)

Analgesia may be produced in certain stressful situations. Exposure to a variety of painful or stressful events produces an analgesic reaction. This phenomenon is called stress induced analgesia (SIA). SIA has been thought to provide insight into the psychological and physiological factors that activate endogenous pain control and opiate systems. For example, soldiers wounded in battle or athletes injured in sports events sometimes report that they do not feel pain during the battle or game; however, they will experience the pain later after the battle or game has ended. It has been demonstrated (in animals) that electrical shocks cause stress-induced analgesia. Based on these experiments, it is assumed that the stress the soldiers and the athletes experienced suppressed the pain which they would later experience.

It has been suggested that endogenous opiates are released in response to stress and inhibit pain by activating the midbrain descending system. Moreover, some SIA exhibited cross tolerance with opiate analgesia, which indicates that this SIA is mediated via opiate receptors. Experiments using different parameters of electrical shock stimulation demonstrate that such stress produces analgesia and some of these stresses that produce analgesia could be blocked by the opioid antagonist naloxone,

whereas others were not blocked by naloxone. These observations lead to the conclusion that both opiate and non-opiate forms of SIA exist.

8.4 Summary

The modulation of pain by electrical brain stimulation results from the activation of descending inhibitory fibers, which modulate (block) the input and output of laminae I, II, V and VII neurons. The route from the PAG to the spinal cord is not direct. It appears to involve a link with the 5-HT-rich raphe nuclei, as well as norepinephrine (NE) from the locus coeruleus (LC) and dopamine (DA) from the ventral tegmental area (VTA). Axons from the raphe nuclei, locus coeruleus and VTA project to the spinal cord dorsal horn by way of the DLF to terminate in lamina I, II and IV to VII (i.e., stimulation of NRM, VTA and LC inhibits the neuronal activity of lamina I, II and IV to VII neurons).

Opioid and serotonergic antagonists reverse both local opiate analgesia and brain-stimulation produced analgesia. This suggests that OA and SPA are produced via the same descending inhibitory system.

In conclusion, in the CNS, much of the information from the nociceptive afferent fibers results from excitatory discharges of multireceptive neurons. The pain information in the CNS is controlled by ascending and descending inhibitory systems, using endogenous opioids, or other endogenous substances like serotonin as inhibitory mediators. In addition, a powerful inhibition of pain-related information occurs in the spinal cord. These inhibitory systems can be activated by brain stimulation, intracerebral microinjection of morphine, and peripheral nerve stimulation. Centrally acting analgesic drugs activate these inhibitory control systems. However, pain is a complex perception that is influenced also by prior experience and by the context within which the noxious stimulus occurs. This sensation is also influenced by emotional state. Therefore, the response to pain varies from subject to subject.

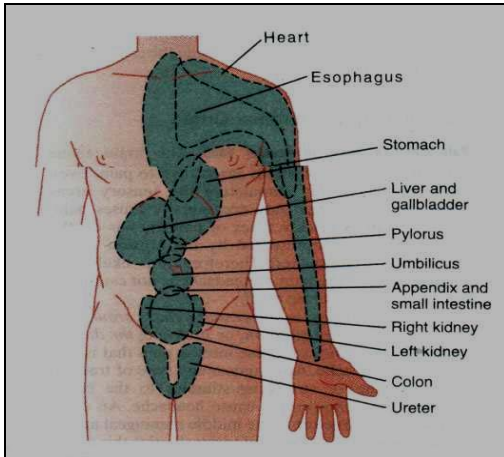
Control questions:

Initial level of the knowledge

1. Anatomy of the Spinal cord
1. The types of Pain and their qualities – fast Pain and slow Pain.
2. Pain receptors and their stimulation:
 - a). pain receptors are free nerve endings;
 - b). three types of stimuli excite Pain receptors – mechanical, thermal and chemical;
 - c). nonadapting nature of Pain receptors.
3. Rate of tissue damage as a stimulus for Pain:
 - a). special importance of chemical Pain stimuli during tissue damage;
 - b). tissue ischemia as cause of Pain;
 - c). muscle spasm as cause of Pain.
4. Pain suppression (“Analgesia”) System in the Brain and Spinal cord:
 - a). Brain’s Opiate system – Endorphins and Enkephalins;
 - b). Inhibition of Pain transmission by simultaneous active sensory signals;
5. Referred Pain and Visceral Pain:
 - a). causes of true visceral Pain (ischemia; chemical stimuli; spasm of Hollow viscus; over distention of a Visceral Pain; intensive viscera)
 - b). ”Parietal Pain” caused by visceral Disease;
6. Headache:
 - a). ... of intracranial origin;
 - b). extracranial types of Headache.

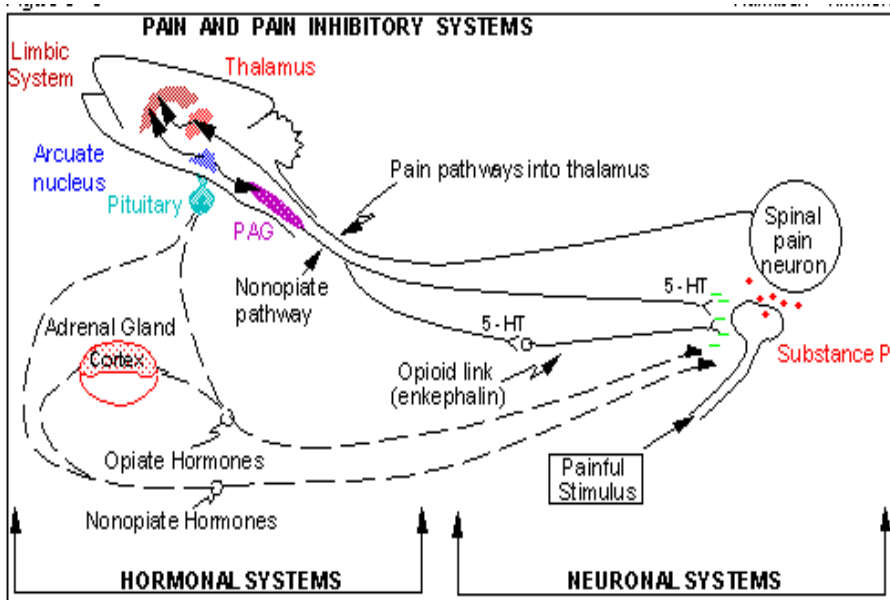
Practical skills

TASK1. Look at these figures. Write the explanations about the reasons for referred pain. Put information about the sites of referred pain in this table.



| organ | region of referred pain |
|-------------------------------|-------------------------|
| Heart | |
| Esophagus | |
| Stomach | |
| liver and goldbladder | |
| appendix and small intenstine | |
| right kidney | |
| left kidney | |
| colon | |
| Ureter | |

TASK 2. Look at these figures. Write the explanations about the pain inhibitory system. Put information in this table.



| Hormonal pain inhibitory system | | Neuronal pain inhibitory system | |
|---------------------------------|--------|---------------------------------|--------|
| Substance | action | Substance | action |
| | | | |

TASK3. Look at this figure, note morphologic components for this Pain pathway. Write an explanation of the transmission of pain signals into the hindbrain, thalamus and cortex via (the fast “pricking pain» pathway and the slow “burring pain» pathway).

TASK8. **Look at this figure. Write an explanation about it.** Distribution of curve obtained from a large number of persons showing the minimal skin temperature that will cause pain.

43 44 45 46 47
temperature (C°)

TASK9. Look at this figure “Areas of headache”. Note its morphologic zones and write an explanation about reasons of headache.



TASK10. Write the explanations for clinical tasks

1. What is the hyperesthesia, analgesia, parestesia?

TASK14. The examination of pain.

This experiment is concerned with the fast component (or first pain) of the pain sensation. The stimulus for pain is potential or actual damage to the tissues. Note, however, that in the following experiment very little pressure is needed to elicit this type of pain.

Draw a 3 cm square on the back of one of the subject's hands, and divide it into a 4 squares. Blindfold the subject, or have him close his eyes. Using a blood lancet, or a sharp pin, apply brief and light stimuli within the squares. Map out the pain-sensitive spots within the grids (the areas in between the pain spots will be pain-insensitive). Note that the subject should report with a "yes" when the stimulus elicits pain and not when the stimulus can be detected as causing only touch/pressure sensation. Record your results in the grids drawn in your work book.

Results:

Quizzes:

1. All of the following are released in response to noxious stimulation at the damaged site(s) EXCEPT:

- A. Globulin
- B. Dopamine
- C. Arachnoid Acid
- D. Acetylcholine
- E. Histamine

#

2. C fibers transmit which type of pain?

- A. Pricking pain
- B. Stimulation produced analgesia
- C. Referred pain
- D. Burning pain
- E. Sharp pain

#

3. C fibers are

- A. small myelinated fibers which carry sharp pain
- B. large unmyelinated fibers which carry burning pain
- C. small unmyelinated fibers which carry burning pain
- D. large myelinated fibers which carry sharp pain
- E. large myelinated fibers which carry temperature sensation

#

4. Aspirin acts to block the formation of

- A. Bradykinins
- B. Prostaglandins

- C. Histamine
- D. Dopamine
- E. Serotonin

#

5. A delta fibers transmit primarily
- A. burning diffuse pain information
 - B. pricking localized pain information
 - C. aching diffuse pain information
 - D. visceral pain information
 - E. phantom pain information

#

6. Pain receptors/nociceptors are
- A. bipolar cells
 - B. free nerve endings
 - C. epithelial receptors
 - D. Pacinian corpuscles
 - E. Meissner corpuscles

#

7. A. two different pain receptors
- B. two different pathways, differing in the number of the synapses
 - C. two different fibers which conduct the impulses at different velocities
 - D. two different neurotransmitters
 - E. two different neuropeptides

#

8. A delta fibers transmit which type of pain to VPL?
- A. Pricking pain

- B. Deep pain
- C. Visceral pain
- D. Burning pain
- E. Aching pain

#

9. Sharp pain, induced by a skin cut for example, is classified by

- A. Burning pain
- B. Aching pain
- C. Somatic pain
- D. Pricking pain
- E. Visceral pain

#

10. A surgeon attempting to treat chronic pain from the pelvic region will suggest to make a lesion in the:

- A. somatosensory cortex
- B. ventroposterior medial thalamus
- C. anterior white commissure
- D. dorsal column
- E. anterior lateral funiculus

#

11. In Brown-Sequard syndrome:

- A. Tactile and pain sensation are lost contralaterally at different levels below the lesion.
- B. Thermal sensation is lost in the ipsilateral side above the lesion.
- C. Kinesthetic and tectile senses are lost ipsilaterally below the lesion.
- D. The withdrawal reflex is lost.
- E. Atrophy is developed in the muscles below the lesion.

#

12. Sharp localized pain is transmitted by:

- A. archispinothalamic tract
- B. Paleospinothalamic tract
- C. Neospinothalamic tract
- D. Sympathetic nerves
- E. Parasympathetic nerves

#

13. Select the best answer: Pain impulses arising within the abdominal and thoracic cavities may reach the CNS by:

- A. somatic nerves innervating
- B. sympathetic nerves
- C. parasympathetic nerves
- D. none of the above
- E. all of the above

#

14. At the level of the ventral trigeminothalamic tract, pain fibers are generally crossed or uncrossed?

- A. Crossed
- B. Uncrossed

#

15. Cell bodies of first order pelvic visceral pain fibers are found in:

- A. dorsal root ganglion
- B. mesenteric ganglion
- C. superior cervical ganglia
- D. inferior cervical ganglion

E. middle cervical ganglion

#

16. The following pathway is sectioned in a chordotomy for the treatment of pain:

- A. Lateral spinothalamic tract
- B. Ipsilateral dorsal column
- C. Corticospinal tract
- D. Spinocerebellar pathway
- E. Spino-olivary tract

#

17. According to the descending pain suppression theory,

- A. Descending spinothalamic fibers produce presynaptic inhibition of Rexed lamina VII neurons.
- B. Pain stimuli activate descending fibers in the dorsolateral fasciculus.
- C. Mechanical stimulation produces descending postsynaptic inhibition of Rexed lamina VIII neurons.
- D. Transection of the dorsal column blocks the descending fibers producing analgesia.
- E. Descending corticospinal fibers produce postsynaptic inhibition of nociceptive spinal neurons will not affect pain sensation.

#

18. The Melzack-Wall gate theory refers to:

- A. Ascending pain suppression system.
- B. Non-noxious input suppresses pain at the spinal cord.
- C. Electrical stimulation-produced analgesia.
- D. Cortical control system suppresses pain.
- E. Descending pain suppression system.

#

19. Electrical stimulation in the periaqueductal gray elicits:

- A. Circular movement
- B. Analgesia
- C. Catatonia
- D. Tremors
- E. Hyperactivity

#

20. The following nuclei are involved in the serotonergic descending modulation system of pain:

- A. Locus coeruleus
- B. Central gray
- C. Ventral trigeminal area
- D. Raphe nuclei
- E. Ventro-posterior medial thalamus

#

21. Nociceptors (pain receptors) include what type of nerves?

- A. Group I
- B. Group II
- C. Group III
- D. Group IV
- E. more than one of the above

#

22. The fact that different thermoreceptors have overlapping receptive fields allows us to respond to a range of temps

- A. True
- B. False

#

23. Thresholds are ____ for touch and temperature and ____ for pain.

- A. high; low
- B. high; high
- C. low; high
- D. low; low

#

24. When there is damage to cells, the cells will release lots of ____ which will then stimulate the nociceptors.

- A. Na
- B. K
- C. Cl
- D. H

#

25. Pain, temperature and touch information synapses in the _____ horn of the spinal cord in either the _____ or _____

- A. ventral horn; substantia gelatinosa; nucleus proprius
- B. dorsal horn; substantia gelatinosa; nucleus proprius
- C. ventral horn; gracile fasciculus; cuneate fasciculus
- D. dorsal horn; substantia gelatinosa; nucleus proprius

#

26. Central connections (body) for pain and temp is sent through the _____ tract to the ____ of the thalamus.

- A. Spinothalamic ; VPM
- B. Trigeminothalamic; VPM

C. Spinothalamic; VPL

D. Trigeminothalamic; VPL

#

27. Central connections (for the head) synapse first in the spinal cord

A. True

B. False

#

28. The trigeminothalamic tract synapses in the ____ of the thalamus

A. VPL

B. VPM

C. post central gyrus

D. reticular formation

#

29. The trigeminothalamic tract sends info to the:

A. hypothalamus

B. Brodmann area 3,1,2

C. reticular formation

D. all of the above

E. 2 of the above

#

30. The homonculus motor cortex is on the _____ and the homonculus sensory cortex is on the _____

A. post central gyrus; pre central gyrus

B. pre central gyrus; post central gyrus

#

31. Pain in an area where a limb has been amputated is referred to as...

- A. Imaginary pain
- B. Sheer pain
- C. Invisible pain
- D. Phantom pain

#

32. What causes us to feel pain?

- A. Nerve endings
- B. The brain
- C. Both of the above
- D. Neither of the above

#

33. The terms "arthralgia" and "neuralgia" refer to pain located where?

- A. Joints and teeth
- B. Arteries and nerves
- C. Joints and nerves
- D. Joints, nerves, arteries, and teeth

#

34. The medical community measures pain on a scale of...

- A. Zero to 10
- B. One to 30
- C. Zero to 50
- D. One to 100

#

35. The pain reliever morphine is derived from which substance?

- A. Lead

- B. Opium
- C. Sugar
- D. Lithium

#

36. If you are in a state of analgesia, you are...

- A. Unable to stop pain
- B. Unable to feel pain
- C. Unable to locate pain
- D. Medically in shock because of pain

#

36. Some people say they feel pain in their hair.

- A. True
- B. False

#

37. Pain is always a sign that something is wrong.

- True
- False

#

38. Redheads may be more sensitive to pain than people with other hair colors.

- A. True
- B. False

#

39. The most common painful condition is:

- A. Headache
- B. Low back pain

C. Cancer pain

D. Arthritis

#

40. Growing pains are real.

A. True

B. False

#

41. Weather changes can trigger pain for people with:

A. Asthma

B. Arthritis

C. Migraine headaches

D. All of the above

#

42. Women have a higher threshold for pain.

A. True

B. False

#

43. The difference between chronic pain and acute pain is:

A. The intensity of the pain

B. How long the pain lasts

C. Where the pain is

D. When the pain comes on

#

44. Exercise can help reduce pain over time.

A. True

B. False

#

45. Icing a sprain:

- A. Returns soft tissue to normal
- B. Decreases swelling
- C. Increases circulation

#

46. If you have arthritis, you have:

- A. Any of a group of more than 100 medical conditions
- B. A condition that only affects seniors
- C. A condition that never affects children

#

47. Positive thinking about pain:

- A. Can reduce pain-related activity in the brain
- B. Has no impact
- C. Makes pain worse

#

48. Mr. John Thomas experiences visceral pain around the upper left lung. All of the following carry this nociceptive information EXCEPT the:

- A. somatic nerves
- B. paleospinothalamic tract
- C. sympathetic nerves
- D. neospinothalamic tract
- E. archispinothalamic tract

#

49. A toothache can be a symptom of:

- A. Eczema
- B. Sinusitis
- C. Alopecia
- D. Hyperthyroidism

#

50. Cell bodies of first order pelvic visceral pain fibers are found in:

- A. dorsal root ganglion
- B. mesenteric ganglion
- C. superior cervical ganglia
- D. inferior cervical ganglion
- E. middle cervical ganglion

#.

51. Stimulation of nociceptors results in the sensation of

- A. Touch
- B. Light
- C. Pain
- D. Heat
- E. Cold

#

52. Where is the right answer? The center of Pain sensation is in the

- A. anterior nerve root ganglia
- B. posterior nerve root ganglia
- C. Cerebellum
- D. Midbrain
- E. post central gyrus of parietal cortex

#

53. The doctor diagnosed a referred pain at the left part of arm and shoulder. What visceral organ can be in hurt?

- A. Diaphragm
- B. Kidney
- C. Heart
- D. Testis
- E. Gallbladder

#

54. Which of the following is true about visceral pain?

- A. It is stimulated by cutting
- B. It is stimulated in organs
- C. It is easily pinpointed
- D. It is stimulated by hot or cold
- E. all of the above

#

55. The hypersensitivity to pain is.....

- A. Analgesia
- B. Paralgesia
- C. Hyperalgesia
- D. Hypoalgesia
- E. Parasthesia

#

56. The Pain receptors are:

- A. Free nervous endings
- B. Pachini bodies
- C. Merkel disks

- D. Rufini bodies
- E. Pacini bodies and Merkel Disks

#

57. Naked nerve endings are the terminal ends of dendrites of sensory neurons and are responsible for which of the following sensations?

- A. Pain
- B. Pressure
- C. Limb position
- D. None of the above
- E. all of the above

#

58. Where is a right answer? The first order neurones of Pain sensation from skin are the cells in the

- A. anterior nerve root ganglia
- B. posterior nerve root ganglia
- C. Cerebellum
- D. midbrain
- E. post central gyrus of parietal cortex

#

59. The doctor diagnosed a referred pain at the patient's epigastric region. What visceral organ can

be in hurt?

- A. Diaphragm
- B. Kidney
- C. Heart
- D. Testis
- E. Gallbladder

#

60. The abnormal pain sensation is

- A. Analgesia
- B. Paralgesia
- C. Hyperalgesia
- D. Hypoalgesia
- E. Parasthesia

#

61. What is a dermatome?

- A. This is a special zone of the lobe cortex
- B. This is a segmental field of the skin which is innervated by a spinal nerve
- C. This is a special zone of the parietal cortex
- D. This is a thoracic zone of the skin
- E. This is a lumbar zone of the skin

#

62. This type of pain can occur both in the skin and in almost any deep tissue and organ...

- A. Acute pain
- B. Electric pain
- C. Throbbing pain
- D. Pricking pain
- E. Sharp pain

Correct answers:

1 – B, 2 – D, 3 – C, 4 – B, 5 – B, 6 – B, 7 – C, 8 – A, 9 – B, 10 – E,

11 – C, 12 – C, 13 – A, 14 – A, 15 – A, 16 – A, 17 – D, 18 – B, 19 – B, 20 – D,

21 – B, 22 – A, 23 – C, 24 – B, 25 – B, 26 – C, 27 – B, 28 – B, 29 – D, 30 – D,

31 – D, 32 – C, 33 – C, 34 – A, 35 – B, 36 – B, 37 – B, 38 – A, 39 – B, 40 – A,

41 – D, 42 – B, 43 – B, 44 – A, 45 – B, 46 – A, 47 – A, 48 – D, 49 – B, 50 – A.

51 – C, 52 – E, 53 – C, 54 – A, 55 – C, 56 – A, 57 – A, 58 – B, 59 – E, 60 – B, 61 – B,

62 – C.

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