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Leading article

Functional neuroanatomy of nociception and pain

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Abstract

Pain is a complex sensory state based on the integration of a variety of nociceptive inputs processed centrally through many parallel and overlapping neural systems. The traditional anatomical concept implies that nociceptive information is dominantly used to generate and regulate perception of pain through one major sensory pathway. It becomes recognized that experiencing the affective component of the pain is at least as important as perception. Also, nociceptive information is strongly influencing brain centers for regulating homeostasis. So, understanding neuroanatomical organization of central processing of nociceptive information is of great clinical importance. There is an attempt to simplify this complex set of interacting networks to a core set of brain regions or a generalizable pain signature. Herewith we wish to give a short overview of recent advances by presenting principles about neuroanatomical organization for processing various aspects of nociceptive inputs.

GENERAL NEUROANATOMICAL PRINCIPLES IN NOCICEPTIVE PROCESSING

Pain is the most distinctive of all the sensory modalities *(1)* but can be simply defined as the subjective experience associated with actual or potential tissue damage *(2–5).* It serves an important protective function and warns to avoid or treat injury. The perception of pain is subjective and can vary greatly among individuals. Moreover, in the same individual an identical sensory stimulus can elicit quite distinct conscious responses under different conditions. This includes also psychological conditions, such as fear or anxiety that can significantly influence the experience of pain. So, more than most sensory modalities, the perception of pain is influenced by emotional state and environmental contingency, is dependent on experience, and varies so markedly from person to person *(6–16),* and consequently remains notoriously difficult to treat .

Noxious stimuli, including tissue injury, activate nociceptors (from the Latin, noceo = to injure, hurt) which are present in peripheral structures and transmit information to the CNS: from the body to the spinal cord dorsal grey column, from the skin of the head to the spinal and principal trigeminal nucleus, and from the neck mucosa to the lower 2/3rd of solitary tract nucleus *(17–19).* To generate perception of pain the information should continue ultimately to the cerebral cortex. From anatomical point of view it should be noted that nociception refers to the process through which information about peripheral stimuli is transmitted by primary afferent nociceptors to the spinal cord, brainstem, thalamus, and subcortical structures. For the experience of pain, activity of thalamocortical networks that process the information conveyed by pathways of nociception is needed *(20–26)* (Figure 1).

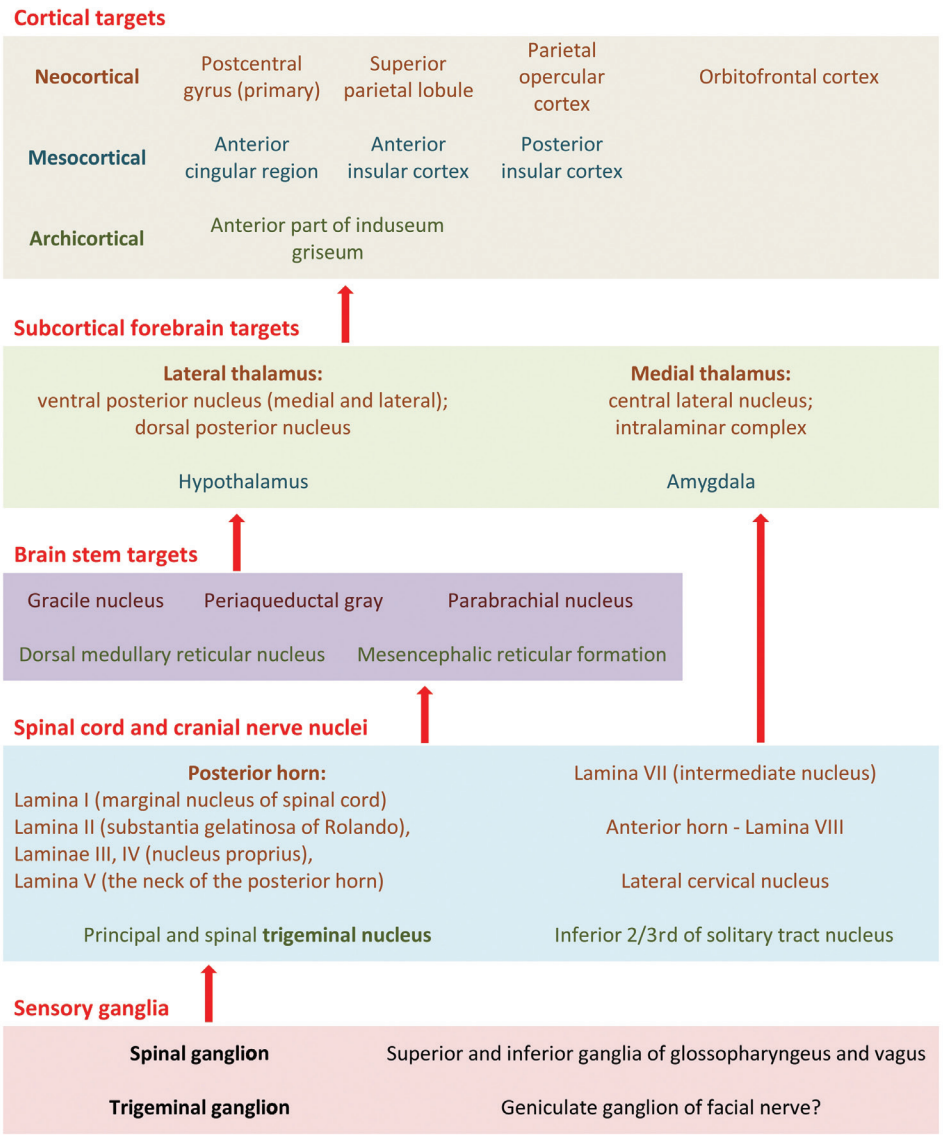

Figure 1. *Structures containing neurons processing nociception and pain.*

Pain sensation is not the direct expression of a sensory event. It has strong urgent and primitive quality with affective and emotional components *(7; 26–32),* and has also influence on homeostatic functioning *(33; 34).* By classical neuroanatomical description pain processing is dominantly related to spino- and trigemino-thalamic pathway *(17–19),* still this pathway is evolutionary newest in conducing nociceptive information *(35).* Pain is actually a complex sensory state that reflects the integration of many sensory signals and is the product of elaborate brain processing. Particularly complex processing is needed for experiencing the affective component of the pain and for the influencing on homeostasis. Numerous parallel and overlapping neural systems processing nociceptive information allow such a complex impact on the brain functioning *(22; 36–40).* Among the ascending pathways arising from the spinal cord and its trigeminal homologue are the spinothalamic and spinoreticulothalamic tracts, as well as the spinoparabrachial-amygdala pathway, which provides more direct access to limbic emotional circuits in the brain. There is an attempt to simplify this complex set of interacting networks to a core set of brain regions or a generalizable pain signature. Such approaches identify the following areas as key to experiencing pain: the thalamus, the posterior and anterior insula, the postcentral gyrus, the anterior cingulate cortex, and the periaqueductal gray matter. Functional specificity of this complex pattern is still unresolved.

Altogether, understanding neuroanatomical organization of central processing of nociceptive information is of great clinical importance *(41-45).* Herewith we wish to give a short overview of recent advances in under-

TABLE 1

Various classes of nociceptors associate with specific function in the detection of distinct pain submodalities.

Modality	Submodality	Nociceptors/fibers
Nociceptive Pain (somatic or visceral)	sharp cutting pain	mechanical nociceptors Aδ fibers
	dull burning pain	polymodal nociceptors C fibers
	deep aching pain from viscera	visceral nociceptors Aδ, C fibers
	burning pain	thermal-mechanical (hot) Aδ fibers
	freezing pain	thermal-mechanical (cold) C fibers
Non-Nociceptive Pain (neurophatic or symphatetic)	complex regional pain syndrome	no nociceptors
	post-herpetic neuralgia	
	phantom limb pain	
	anesthesia dolorosa	

standing neuroanatomical organization for various aspects of nociceptive processing and to relate neural structures and pathways to various submodalities of nociceptive processing.

MOLECULAR ANATOMY OF PERIPHERAL NOCICEPTIVE PROCESSING

Nociceptors, structures that respond selectively to stimuli that can damage tissue are widely distributed in the skin and deep tissues and include thermal, mechanical, and polymodal sensory receptors *(46-49).* They respond directly to mechanical and thermal stimuli, and indirectly to other stimuli by means of chemicals released from cells in the traumatized tissue. Fourth class, so called "silent" nociceptors are found in the viscera. The nociceptors are free nerve endings of the peripheral axonal branches originating from primary sensory neurons. The cell bodies of nociceptors that convey information from the body are located in the dorsal root ganglia. Trigeminal ganglia and superior ganglia of glossopharyngeus and vagus contain somatic neurons processing nociceptive stimuli from skin, cranial periost and dura, the mucosa of eye, nasal sinuses, oral and nasal cavity and possibly part of tympanic tube and cavity. For the rest of tympanic tube and cavity, and the whole mucosa of pharynx and larynx primary visceral neurons are located in the inferior ganglia of glossopharyngeus and vagus *(17).* The central branches of these primary neurons enter the central nervous system through spinal or cranial nerves where they make synaptic connections with a complex array of neurons that play different roles in nociceptive processing and pain. Trigeminal, glossopharyngeal and vagal nerve convey somatic information into the trigeminal nuclei, and visceral information into the nucleus of the solitary tract. The spinal nerve conveys nociceptive information from the body and viscera and terminates on neurons in the dorsal horn of the spinal cord. Afferent fibers innervating viscera project to the CNS through autonomic nerves; some spinal afferents travel along hypogastric, lumbar colonic and splanchnic nerves to terminate in thoracolumbar regions as part of sympathetic innervation, while vagal and pelvic afferents respectively terminate in the brainstem and lumbosacral cord and contribute to parasympathetic innervation. Thoracic branches of vagus also contain afferent fibers, but the nature to conduct pain information from thoracic and abdominal viscera is not clarified.

Based on the myelination of their afferent fibers nociceptors in the skin, muscle, joints, and visceral receptors fall into two broad classes *(2; 50-52).* The first class are small diameter, thin myelinated Aδ fibers that innervate nociceptors producing short-latency pain described as sharp and pricking. The majority are mechanoreceptors because they are activated by sharp objects that penetrate, squeeze, or pinch the skin. In addition, many of these Aδ fibers also respond to noxious heat that can burn the skin. Electrophysiological studies have subdivided Aδ nociceptors into two main classes: type I and type II. Type I respond to both mechanical and chemical stimuli, but have relatively high heat thresholds (>50°C). These fibers mediate the first pain provoked by pinprick and other intense mechanical stimuli. Type II Aδ nociceptors have a much lower heat threshold, but a very high mechanical threshold; these fibers mediate the "first" acute pain response to noxious heat. The second class are nociceptors innervated by small diameter, unmyelinated C fibers producing diffusely distributed and poorly tolerated dull, burning pain. Under this heterogeneous class the most common type are polymodal nociceptors activated by a variety of noxious mechanical, thermal, and chemical stimuli, such as

pinch or puncture, noxious heat and cold, and irritant chemicals applied to the skin. Electrical stimulation of these fibers in humans evokes prolonged sensations of burning pain. Of particular interest are the heat responsive, but mechanically insensitive unmyelinated afferents (so-called silent nociceptors) that develop sensitivity when the chemical milieu of inflammation alters their properties *(53)*.

Visceral fibers can serve sensory function and evoke conscious sensations and also afferent function and regulate autonomic flow. Visceral sensory afferents are almost exclusively thinly myelinated Aδ-fibres and unmyelinated C-fibres. However, the distinction between nociceptive afferents and non-nociceptive afferents in the viscera is not clear. Nociceptors in the viscera that produce sensations of intense pain are activated by distension or swelling. Silent nociceptors found in the viscera are not normally activated by noxious stimulation. However, after tissue insult these nociceptors "wake up" in response to endogenous chemical mediators associated with tissue injury. Silent nociceptors are typically associated with increased spontaneous activity and responsiveness to noxious and even innocuous stimulus intensities. Their activation is thought to contribute to the development of secondary hyperalgesia and central sensitization, two prominent pain syndromes.

The membrane of the nociceptor contains protein complexes forming receptors and channels that transduce thermal, mechanical, or chemical energy of noxious stimuli into electrical impulses, which are propagated along the peripheral and central axon of the nociceptor into the central nervous system. Biochemical and molecular analysis of the nociceptor has identified multiple nociceptor subclasses, each expressing a distinctive repertoire of membrane ion channels, receptors and intracellular signaling proteins that are attractive targets for the development of drugs for therapeutic intervention in clinical pain conditions *(54-56)*. This includes voltage-gated sodium, potassium and calcium channels, leak channels, and ligand-gated channels such as acid-sensing ion channels and transient receptor potential (TRP) channels *(57)*. The role of transient receptor potential ion channels in thermal sensation was originally discovered by analyses of natural substances such as capsaicin and menthol that produce burning or cooling sensations when applied to the skin or injected subcutaneously. Capsaicin, the active ingredient in chili peppers, has been used extensively to activate nociceptive afferents that mediate sensations of burning pain *(58)*. The varieties of TRP channels in nociceptors underlie the perception of a wide range of temperatures from extreme cold to intense heat. Some classes of TRP receptors are activated by cold temperatures and inactivated by warming (TRPM8 and TRPA1receptors) while some types of TRP receptors are activated by warm or hot temperatures and inactivated by cooling (TRPV3, TRPV1, TRPV2 and TRPV4 receptors) *(59-61)*. A key role in the perception of pain in humans plays the voltage-gated sodium channel NaV1.7, found exclusively in the periphery and its mutation can lead to the inability to experience pain *(62)*. An ionotropic purinergic receptor, PTX3, that is activated by adenosine triphosphate (ATP) released from peripheral cells after tissue damage is also expressed by nociceptors *(63-65)*. In addition, nociceptors express members of the Mas-related G protein-coupled receptor (Mrg) family, which are activated by peptide ligands. They serve to sensitize nociceptors to other chemicals released in their local environment *(66-68)*.

Neuroanatomical and molecular characterization of nociceptors demonstrated their heterogeneity; various functionally and molecularly heterogeneous classes of nociceptors associate with specific function in the detection of distinct pain submodalities *(69)*.

MECHANISMS MODULATING NOCICEPTIVE PROCESSING

The proper function of the nociceptive system enables and enforces protective behavioral responses such as withdrawal or avoidance to acutely painful stimuli. In case of an injury the vulnerability of the affected tissue is going to increase *(70-75)*. The nociceptive system adapts to this enhanced vulnerability by locally lowering the nociceptive thresholds and by facilitation of nocifensive responses. The behavioral correlates of these adaptations are allodynia (condition in which non-noxious events are perceived as noxious) and hyperalgesia (mildly noxious events are perceived as highly noxious). However, hyperalgesia and allodynia may persist long after the initial cause for pain or may occur due to dysfunction of parts of the peripheral or central nervous system and become maladaptive rather than protective.

Two types of hyperalgesia, primary and secondary, are associated with different mechanisms. Primary hyperalgesia develops at the site of tissue injury associated with an increased sensitivity of the peripheral nerve fibers involved in pain. Secondary hyperalgesia develops in uninjured tissue surrounding the site of injury. This form of hyperalgesia is not caused by sensitization of nociceptive nerve endings but due to changes in the excitability of neurons in the central nervous system, including the spinal cord and supra-spinal sites in the brain. Recent evidence suggests, however, that altered processing in the central nervous system is equally important in the induction of primary hyperalgesia *(70)*.

Numerous mediators in the peripheral and central nervous systems contribute to the processes of sensitization. The sensitization of nociceptors is triggered by chemical mediators released from distinct cell types that accumulate at the site of tissue injury and act together to decrease the threshold of nociceptor activation, such as histamine, anandamide, acetylcholine, serotonin, norepinephrine,

prostaglandin, bradykinin, substance P and calcitonin gene-related peptide. Central sensitization is a considerably more complicated process that can result from increased release of excitatory neurotransmitter (e.g., glutamate, substance P) and/or enhanced synaptic efficacy. These changes relate to several cellular mechanisms (a) presynaptic changes, (b) postsynaptic changes, (c) interneuron changes, (d) changes in descending modulation, and (e) immune/microglial mechanisms *(76; 77)*.

The understanding of pain mechanisms and pain control has focused on the properties of primary afferent and dorsal horn nociceptive neurons and ascending pathways. However, there is an active regulation of sensory transmission at the level of the dorsal horn by descending projections arising from a number of brain sites *(78-89)*. Descending control plays a critical role in determining the experience of pain and can be facilitatory as well as inhibitory. The balance between inhibition and facilitation is dynamic, and can be altered in different behavioral, emotional and pathological states. For example, intense stress and fear are associated with decreased responsiveness to noxious stimuli that reflects a shift towards descending inhibition. By contrast, inflammation and nerve injury, sickness, and chronic opioid administration are associated with hyperalgesia that in part reflects a shift towards descending facilitation. There is much evidence to suggest that descending facilitation of spinal nociception is a major contributor to central sensitization and the development of secondary hyperalgesia.

Descending control arises from a number of supraspinal sites, including the midline periaqueductal gray-rostral ventromedial medulla (PAG-RVM) system, and the more lateral and caudal dorsal reticular nucleus (DRt) and ventrolateral medulla (VLM). Serotonergic neurons settled in the raphe nuclei and neorepinephrine neurons settled in the locus coerlues play the major role in descending control. Inhibitory control from the PAG-RVM system preferentially suppresses nociceptive inputs mediated by C-fibers, preserving sensory-discriminative information conveyed by more rapidly conducting A-fibers. Analysis of the circuitry within the RVM reveals that the neural basis for bidirectional control from the midline system is two populations of neurons, ON-cells and OFF-cells that are differentially recruited by higher structures important in fear, illness and psychological stress to enhance or inhibit pain.

FUNCTIONAL NEUROANATOMY OF CENTRAL NOCICEPTIVE PROCESSING

The pain-related circuitry extends over both the cognitive and the emotional-motivational domains of the brain. It includes the spinothalamic component of the anterolateral fasciculus, the trigeminothalamic tract and pathways that connect the spinal cord and the sensory nuclei of the trigeminal nerve with the brain stem, the hypothalamus and the basal forebrain *(17)*.

The central branches of primary neurons enter the central nervous system and make synaptic connections with a complex array of neurons. This triggers the release of neurotransmitters such as glutamate and substance P, which activate second-order neurons that project to the brain. The spinal gray dorsal horn-column (and its equivalent, the caudal part of trigeminal nerve nucleus) constitutes one of the main relay stations for primary afferents of the dorsal roots.

Besides nociceptive-specific neurons, the spinal dorsal horn (especially deeper laminae) also contains wide dynamic range (WDR) neurons that respond to both innocuous and noxious stimuli. After entering the spinal cord (through lateral division of peripheral nerve) small myelinated Aδ and unmyelinated C fibers terminate in the dorsal horn. The spinal gray matter in the dorsal horn is divided into six layers of cells *(90-93)*. Nociception specific neurons in the lamina I respond selectively to noxious inputs from Aδ or C fibers and project to higher brain structures. Other classes of lamina I responed to both innocuous and noxious mechanical stimulation and thus are termed wide-dynamic-range neurons. Neurons in laminae II and III are interneurons that receive inputs from Aδ and C fibers, and make excitatory or inhibitory connections to neurons in lamina I, IV, and V that project to higher brain centers. Wide-dynamic-range neurons in lamina V typically respond to a wide variety of noxious stimuli and project to the brain stem and thalamus. Neurons in lamina V also receive input from nociceptors in visceral tissues.

Many neurons located in laminae VII and VIII, building the intermediate grey and deep part of ventral gray column, have complex response properties to noxious stimuli because the inputs from nociceptors to these neurons are conveyed through many intervening synapses. Whereas most dorsal horn neurons receive unilateral input, neurons in lamina VII often respond to stimulation of both side of the body and therefore contribute to the diffuse quality of many pain conditions. Visceral C fibers terminate ipsilaterally in laminae I, II, V, and X and also in lamina V and X of the contralateral gray matter.

Finally, fibers from lamina I and the nucleus of the solitary tract convey information about impending and actual tissue damage, and a wide range of visceral stimuli; the responses of neurons in lamina V correlate closely with reports of pain intensity, while the lamina VII plays a significant role in emotional responses to sensory stimuli.

Five major ascending pathways contribute to the central processing of nociceptive information: the spinothalamic, spinoreticular, spinomesencephalic, cervicothalamic, and spinohypothalamic tracts.

From neurons in laminae I, V, and VII, the main targets of the small-diameter fibers with sensory information destined for conscious perception, originates the spinothalamic tract that is the principal pathway transmitting noxious, thermal, and visceral information to the thalamus and cerebral cortex *(94).* The axons of most neurons in lamina I cross the midline, just ventral to the central canal, and ascend in the contralateral lateral spinothalamic tract located in the lateral funiculus. Axons of lamina V neurons cross the spinal cord and ascend in the contralateral ventral spinothalamic tract. Axons from the caudal part of spinal trigeminal nucleus form tractus trigeminothalamicus lateralis that crosses the midline and joins the spinothalamic tract. As a result of the decussation of spinothalamic fibers in the spinal cord, noxious information from each dermatome is transmitted contralaterally in the anterolateral column. The importance in pain processing through the sphinothalamic tract is demonstrated by experimental and clinical evidence. Electrical stimulation is sufficient to elicit the sensation of pain and anterolateral cordotomy results in a marked reduction in pain sensation on the side of the body contralateral to that of the lesion. As mentioned, information carried by small-diameter sensory fibers also reaches the cerebral cortex through several polysynaptic routes other than the spinothalamic tract *(38-40; 95).* Although many of these pathways originate from neurons in lamina I and V, they arise from a different group of neurons and project to brain stem nuclei which in turn project to the thalamus and to other sites, such as the hypothalamus and amygdala. Neurons that project to sites other than the thalamus are involved in homeostatic control, by regulating endocrine release and autonomic activity. The spinoreticular tract ascends in the anterolateral quadrant of the spinal cord and terminates in both the reticular formation and the thalamus. It contains the axons of projection neurons in laminae VII and VIII and do not cross the midline. The spinomesencephalic (spinoparabrachial) tract projects in the anterolateral quadrant of the spinal cord to the mesencephalic reticular formation and periaqueductal gray matter. It contains the axons of projection neurons in laminae I and V. Information transmitted along this tract are thought to contribute to the affective component of pain. They also course through the dorsal part of the lateral funiculus and project to the parabrachial nucleus. Neurons of the parabrachial nucleus project to the amygdala, a key nucleus of the limbic system that regulates emotional states. The spinohypothalamic tract projects to hypothalamic nuclei that serve as autonomic control centers involved in the regulation of the neuroendocrine and cardiovascular responses that accompany pain syndromes. It contains the axons of neurons in laminae I, V, and VIII. The cervicothalamic tract runs in the lateral white matter of the upper two cervical segments of the spinal cord and contains the axons of neurons of the lateral cervical nucleus, which receives input from neurons in laminae III and IV of the dorsal horn. Most axons in the cervicothalamic tract cross the midline and ascend in the medial lemniscus of the brain stem, terminating in midbrain nuclei and in the ventroposterior nuclei of the thalamus. The signals from nociceptors in the pelvic and abdominal viscera are relayed through other neurons in laminae III and IV of the sacral and midthoracic spinal cord which project axon through the most medial part of the white dorsal column terminating in the gracile nucleus.

The thalamus represents a key integrative structure for the processing of pain and thus contains several relay nuclei that participate in the central processing of nociceptive information.

The lateral nuclear group comprises the ventroposterior medial nucleus, the ventroposterior lateral nucleus, and the dorsal posterior nucleus that receive inputs from nociception-specific and wide-dynamic-range neurons in laminae I and V of the dorsal horn through the spinothalamic tract. The lateral thalamus is thought to be concerned with the processing of information about the precise location of an injury, information usually conveyed to consciousness as acute pain. The medial nuclear group of the thalamus comprises the central lateral nucleus of the thalamus and the intralaminar complex and receives major input from neurons in laminae VII and VIII of the spinal cord. Many neurons in the medial thalamus respond optimally to noxious stimuli and project widely to the basal ganglia and different cortical areas. The pathway to the medial thalamus was the first spinothalamic projection evident in the evolution of mammals and is therefore known as the paleospinothalamic tract. It is also sometimes referred to as the spinoreticulothalamic tract because it includes indirect connections through the reticular formation of the brain stem. The projection from the lateral thalamus to the ventroposterior nuclei is most developed in primates, and is termed the neospinothalamic tract.

Regarding cortical processing it should be emphasized that pain is a complex perception that involves many areas. Spatial, temporal and intensity aspects of pain perception are processed in the primary and secondary somatosensory cortex (S1 and S2, respectively). The anterior cingulate cortex and insular cortex are involved in processing emotional states associated with pain, while the dorsal posterior insula contributes to the autonomic component of pain responses. Moreover, the prefrontal cortex with corresponding mediodorsal thalamic nucleus and premotor areas in connection with cerebellum are also commonly activated by painful stimulation.

FUNCTIONAL NEUROANATOMY OF PAIN SUBMODALITIES

The sense of pain includes a response to external events that damage or harm the body and therefore belongs to

extroceptive sensation. Although the sense of the function of the major organ systems of the body and its internal state (interoception) do not become conscious sensation, abnormal function in major organ systems resulting from disease or trauma can evoke conscious sensations of pain.

When pain is experienced it can be acute, persistent or chronic *(76).* Persistent pain characterizes many clinical conditions and is usually the major reason why patients seek medical attention. In contrast, chronic pain does not serve a useful biological function; it only makes patients miserable *(7; 31; 32; 96-101).* Persistent pain can be subdivided into two broad classes, nociceptive and neuropathic (Table 1). Nociceptive pains result from the direct activation of nociceptors in the skin or soft tissue in response to tissue injury and usually arise from accompanying inflammation. Sprains and strains produce mild forms of nociceptive pain, whereas arthritis or a tumor that invades soft tissue produces a much more severe nociceptive pain. Pain may also result from injury to sensory fibers or from damage to the central nervous system. These types of pain are designated as non-nociceptive or neuropathic pain *(77; 102-105).* Neuropathic pains include the syndromes of reflex sympathetic dystrophy, also called complex regional pain syndrome, and post-herpetic neuralgia, the severe pain experienced by patients after a bout of shingles. Other neuropathic pains include phantom limb pain *(106-109),* the pain that occurs after limb amputation. In some instances pain can even occur without a peripheral stimulus, a phenomenon termed anesthesia dolorosa. This syndrome can be triggered following attempts to block chronic pain, for example after therapeutic transection of sensory afferent fibers in the dorsal roots.

Sharp, pricking pain is produced by nociceptors innervated by Aδ fibers and activated by sharp objects that penetrate, squeeze, or pinch the skin (mechanical nociceptors). Dull, burning pain that is diffusely localized and poorly tolerated is produced by nociceptors innervated by C fiber (polymodal nociceptors). When a stone hits your elbow, you initially feel a sharp, fast, momentary pain, called first pain and conveyed by Aδ fibers followed by a more prolonged aching and sometimes burning pain ("second pain") which is transmitted by the C fibers.

There is a clear demarcation between the perception of innocuous warmth and noxious heat. This enables us to avoid temperatures capable of causing tissue damage. If skin temperature changes slowly, we are unaware of changes in the range 31° to 36°C. Below 31°C the sensation progresses from cool to cold and finally, beginning at 10° to 15°C, to pain. Above 36°C the sensation progresses from warm to hot and then, beginning at 45°C, to pain. The freezing pain is produced by cold nociceptors innervated by C fibers, while the burning pain is produced by heat nociceptors innervated by Aδ fibers. Thermal stimuli activate specific classes of TRP ion channels in the membrane *(60).* Two classes of TRP receptors are activated by cold temperatures and inactivated by warming; TRPM8 receptors respond to temperatures below 25°C (such temperatures are perceived as cool or cold), while TRPA1 receptors have thresholds below 17°C (this range is described as cold or frigid). Four types of TRP receptors are activated by warm or hot temperatures and inactivated by cooling; TRPV3 receptors are expressed in warm type fibers and they respond to warming of the skin above 35°C (generate sensations ranging from warm to hot). TRPV1 and TRPV2 receptors are expressed in heat nociceptors and respond to temperatures exceeding 45°C (mediate sensations of burning pain). TRPV4 receptors are activated by temperatures above 27°C and respond to normal skin temperatures.

Visceral pain (deep aching pain) is sensations of intense, diffuse, often poorly localized pain. Diffuse nature and difficulty in locating visceral pain is due to a low density of visceral sensory innervation and extensive spinal distribution of visceral C fibers. Visceral pain is often associated with marked autonomic phenomena: nausea, gastrointestinal disturbances, pallor, profuse sweating, and changes in blood pressure, heart rate and body temperature. In addition, visceral pain frequently produces referred pain, a condition in which pain from injury to a visceral tissue is perceived as originating from a region of the body surface. Referred pain is sharper, better localized and less likely to be accompanied by autonomic signs, and therefore difficult to differentiate from pain of somatic origin. Convergence of visceral and somatic afferent fibers may account for referred pain phenomenon. Nociceptive afferent fibers from the viscera and fibers from specific areas of the skin converge on the same projection neurons in the dorsal horn (lamina V neurons). Thus, a signal from this neuron does not inform higher brain centers about the source of the input and the brain incorrectly attributes the pain to the skin. Another anatomical explanation for instances of referred pain is that the axons of nociceptive sensory neurons branch in the periphery, innervating both skin and visceral targets *(110; 111).*

There is one unpleasant sensation showing considerable apparent overlap in the neuronal cells and circuits that transmit pain, the itch. It is characterized by a strong innate urge to scratch and is confined to the skin, the ocular conjunctiva, and the mucosa. Itch was considered to be related to pain, because painful stimuli such as scratching inhibits while some analgesics (e.g. opioids) can cause itch. In addition, some itch-causing compounds (pruritogens) induce inflammatory pain, and under certain circumstances some pain-causing compounds (algogens) induce itch. Finally, there is a broad overlap between relevant mediator systems in pain and itch. Parallels between pain and itch processing are even more evident in the pattern of central sensitization. Touch- and pin prick-induced pain (allodynia and punctate hyperalgesia) correlate to touch- and pin prick induced itch (alloknesis and punctate hyperknesis). However, recent discoveries about

molecular and cellular basis of itch cover diverse aspects of itch sensation, from the identification of new receptors to the characterization of spinal cord itch circuits. These studies demonstrate that itch sensory signals are clearly demarcated from input of other somatosensory modalities (pain, touch, temperature) that is achieved by the expression of dedicated receptors and transmitters in a select population of sensory neurons which detect pruritogens. Also, itch specificity is maintained in a spinal cord circuit by the utilization of specific neurotransmitters and cognate receptors to convey input along a distinct cellular pathway *(112-116).*

Recent advances in molecular and anatomical processing of pain: clinical implications

Impressive insights into the molecular mechanisms of peripheral pain transduction has been recently developed opening the way for more effective pain therapies. Human genetics and molecular biology have revealed specific channels expressed selectively by nociceptive sensory neurons, such as TRP and Na channels, what has led to the development of many small-molecule channel antagonists some of which may prove to be effective as selective peripheral analgesics. The use of transcutaneous and dorsal-column electrical stimulation in the control of certain types of peripheral pain was encouraged by the finding that the balance of activity in small- and large-diameter sensory fibers modulates the perception of pain. Also, an observation that stimulation of specific sites in the brain stem produces deep analgesia has encouraged efforts to control pain by activating endogenous modulatory systems. In certain clinical conditions intrathecal and epidural administration of opiates induces a potent analgesia. However, understanding of the organization of central pain circuits under normal and pathological conditions remains relatively incomplete and thereby for most central pain syndromes there are still no effective pain therapies. It is expected that the future progress in pain therapy will depend on the research finding about brain circuits that transmit nociceptive signals *(2; 117-120).*

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