Introduction to Pain

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The International Association Study of Pain (IASP) identifies "pain" as an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage [1]. This definition, first published in Pain Journal in 1979, comes from the works made by Harold Merskey almost 15 years before, that is in 1964.

1.1 Anatomy of Pain Pathways

1. Primary afferent neuron (PAN): begins from the periphery and reaches the spinal cord where it stops in the superficial segments at the synapse with secondary neuron and interneurons. The PAN is represented by a T cell with the body located in the spinal ganglion or in the Gasser ganglion.
2. Secondary neuron can lead the electrical signal throughout the paleo- or neospinothalamic pathway. In the first case there are many synapses before reaching the medial thalamus; in the second case, it arrives immediately to the lateral part of thalamus.
3. Perception and processing take place in the cerebral cortex where pain signal becomes conscious. A pain center does not exist because the entire brain is involved: insula cortex, cingulate cortex, and prefrontal cortex process emotive and cognitive components of pain, instead the somatosensory cortex elaborates sensory components, in particular the localization and the intensity.

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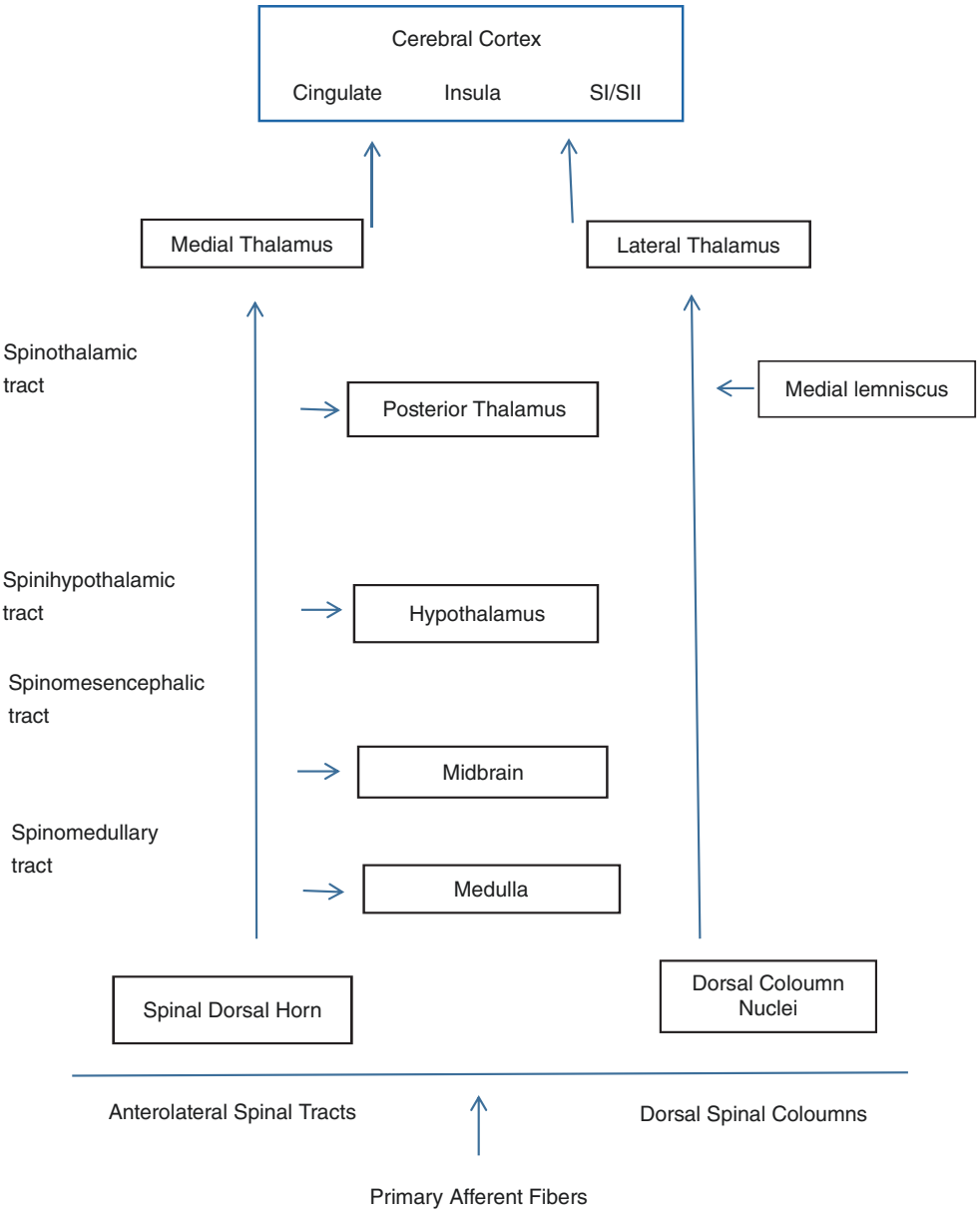

Fig. 1.1 Pain network

4. Descending fibers from the cortex to periaqueductal gray and raphe magnus nucleus reach the spinal cord's interneurons and can modulate the input of the pain signal inside the cenral nervous system [2] (Fig. 1.1).

1.2 Physiology of Pain

Physiology of pain includes:

1. Transmission
2. Modulation
3. Perception and processing
4. Modulation

Transduction occurs at the end of peripheral nerves where pain receptors called "nociceptors" are located. These corpuscles at the primary afferent neuron level are able to convert a mechanical, heating, or chemical stimulus to an electrical signal when the body experience is an injury or an inflammation.

In normal conditions, nociceptors are activated by high-intensity stimuli.

Transmission is the path from the nociceptors to the cerebral cortex through the peripheral nervous system (PNS) and CNS.

Perception and processing include many brain areas that determine location and intensity of pain, add emotional and cognitive component, activate the memory, and consequently influence the behavior.

Modulation: Pain is not transmitted always with the same intensity, but can be modulated in excess or defect by cortical and subcortical structure. These areas are activated by particular situations like stress or placebo in order to face dangerous events for the life.

The most important target is the synapse between primary and secondary afferent neurons; at this level we can act with opioid therapy or with non-pharmacological approach such as TENS or spinal cord stimulation [2].

1.3 Classification of Pain

According to pathophysiology pain can be classified as:

1. Nociceptive pain: caused by physiologic activation of pain receptors; has natural physiologic transduction; can be local and referred pain, is a normal physiological sensation; has a good answer to analgesic therapy [3].
2. Neuropathic pain: caused by an injury or dysfunction in central and peripheral nervous system [4]; is inside a neuroanatomical field; characterized by new and strange sensations, strange and new feelings.

3. Nociplastic pain: arises in the CNS, caused by an imbalance inside the regulatory system of the nociceptive pathway [5].

According to time pain can be classified as:

1. Acute pain: biological function of protection; time limited; single cause.
2. Chronic pain: long lasting; useless; multiple causes; self-sustaining.

In the past chronic pain was considered the symptom of a chronic disease linked to a temporal parameter, it is now considered a disease of its own on the basis of a pathophysiological criterion no longer resolvable. It can be tied to three mechanisms:

1. Mechanism of injury and pain are similar or the same.
2. Pain has its own mechanism in addition to those of the disease.
3. Pain has own mechanism completely different from those that caused the disease.

The transition from acute to chronic pain is a process not still clarified, but many elements can be involved as peripheral inflammation, neuropathic factors, peripheral and central sensitization, psychological and social factors.

Continuous stimulation modifies the nervous system through the mechanism of plasticity with three possible consequences:

- Peripheral sensitization
- Central sensitization
- Cortical reorganization

The nervous system as a whole becomes much more active [6]. Functional magnetic resonance imaging studies have shown that the brain of a person suffering from chronic pain is different from that of an asymptomatic subject: in particular, in the first case the images show hyper neuronal activity.

In acute pain, nociceptors, pain receptors located on the end of peripheral nerves, are activated when the body experiences an injury or an inflammation. The nerves in the periphery send pain signals through the dorsal root ganglion, to the spinal cord and central nervous system. When pain is acute, signaling typically stops once the cause of pain is resolved [7].

However when pain becomes chronic and lasts more than 3 months, repeated stimulations of sensory nerves determine changes to the pathway of pain signals leading to a pathophysiological self-regenerating mechanism where nervous system is sensitized and the perception of pain becomes higher.

Both peripheral and central nervous systems can be sensitized to pain signals in response to injury or inflammation and nociceptors in periphery can increase their sensitivity to painful stimuli; the process is called peripheral sensitization. These sensitized nociceptors consequently send additional pain signals to the central nervous system which can lead to the overstimulation of CNS. This results in a central

sensitization which increases the perception of pain. In this way, central sensitization leads to the perpetuation of pain.

Sensitization starts at the molecular level [8]. In response to an injury or inflammation cells of the site of pain release variety of biochemical mediators including neurotrophin NGF (nerve growth factor), the citochina TNF (tumor necrosis factor), the interleukin IL-1beta, IL-6 (interleukin), and PG E2 (prostaglandin). These mediators bind nociceptors in periphery leading to sensitization on the pain pathway. When the cause of pain continues over time, the persistent activation of the pain pathway leads to increase in the synthesis of glutamate, neuropeptides such as substance P and CGRP, and BDNF [9–12].

Substance P and CGRP enhance the sensitization of the sensory nerves in the periphery. In the CNS, all four of these mediators can be released by the primary afferent neurons subsequently binding in the receptors in the dorsal horn of the spinal cord contributing to the activation of the principal intracells pathway and initiate the central sensitization.

NGF plays a key role in the amplification of the pain signal by sensitizing neurons into pain pathway and causing an overproduction of other pain mediators. It is found throughout the body that levels of NGF increase in respond to injuries or conditions associated with pain. In presence with some conditions associated with chronic pain like osteoarthritis, rheumatoid arthritis, gout, or chronic low back pain, there is a continuous overproduction of NGF. As a result, more NGF is available to bind to peripheral sensory nerves increasing the number of pain signals that trouble from the periphery to the CNS [13–15].

This contributes to the sensitization of the nerves in both peripheral and central nervous system amplifying and perpetuating chronic pain.

The relationship between the periphery and the central nervous system provides a key insight on the chronic pain.

Peripheral sensitization (PNS), central sensitization (CNS), and heightened perception of pain (NEUROMATRIX) are segments of the same phenomenon.

1.4 Conclusion

Around the world one-fifth of people suffer from moderate to severe chronic pain. Chronic pain has a significant negative impact on the quality of the patient's life and in particular can produce sleepiness, decreased activity, and mood changes such as depression, anxiety, anger, and fatigue and through the hypothalamus-hypophysis-adrenal gland axis can cause chronic stress.

Chronic pain therefore changes the way of living: the affected person adapts to the new situation and the pain becomes the center of existence causing avoidance behaviors, social withdrawal, and catastrophism. It is therefore an individual complexity, characterized by a multifactorial experience and a successful therapeutic strategy must include addressing the emotional, cognitive, social aspects and not only somatic pain.

The first phase of treatment must necessarily be the breakdown of pain into its constituent elements, observing, asking, listening, and only after visiting the patient.

The goal is to diagnose pain generator and underlying physiopathological mechanisms, recognize the emotional and cognitive elements, to know the person in front of us, behavior, the social and family environment.

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