Physiology of nociception

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Like most reviews on the pathophysiology of pain this lecture will mainly consider the physiology of nociception.

Nociception like other sensory modalities is subserved by a specific array of nervous connections which have been known in broad lines for many years. A number of neurosurgical operating procedures (cordotomy, tractotomy ...) were based on this knowledge.

In recent years owing to major experimental findings (opioid receptors, endogenous opioid substances ...) and theoretical efforts (gate control theory ...) a new paradigm has emerged for the comprehension of pain. Mechanisms underlying the extraordinary plasticity of human pain are better understood and many new therapeutical approaches have been proposed.

Peripheral mechanisms

The cell body of primary afferent neurons conveying pain sensation are located in the dorsal root ganglion. Their peripheral endings in the skin, muscles, viscera... are directly activated (without specialized receptors) by noxious stimuli.

Free endings from Aβ fibers (small, poorly myelinated, conduction: 4-36 m/s) are activated by strong mechanical stimuli (pinching, pricking). They are responsible for the so called «fast pain», highly localized («sharp pain») and of short duration.

Free endings from C fibers (amelycinic, conduction: 2 m/s) are activated by mechanical, thermal (45°), chemical stimuli (polymodal fibers). C fibers have a high threshold and no spontaneous activity, their receptor fields is small. They can develop sensitization: repeated activation lead to lowering of threshold and enhancement of response for a given stimulus.

The activation of C fibers may be direct from physical mechanisms but the sensitization phenomenon suggests the intervention of chemical substances, the so-called «algogen substances». The role of substance P (liberated by the nerve ending itself) histamin, bradykin, serotonin, K-ions liberated at the pain focus in various circumstances is well established but not entirely understood in details. The role of prostaglandin E generating pain in inflammatory focus explains the therapeutical action of aspirin, corticoïds...

Spinal cord entry and dorsal horn relay

Afferent fibers penetrate the spinal cord through the dorsal root at the level of intermediate lateral sulcus. (However, a relatively large number of pain related amyelinic fibers enter the cord through the ventral root). At the site where dorsal root enter the cord large myelinic fibers are dorso-medial whereas small fibers are ventrolateral: this anatomical disposition allows selective destruction of pain fibers (dorsal root entry zone, operation of Sindou). These fibers bifurcate and ascend or descend for 1 to 3 levels forming part of the Lisauer tract. They enter the dorsal horn and most of them terminate on lamina 1 (marginal layer) and 2 (substantia gelastiosa SG). Other fibers mostly Aβ terminate more deeply on lamina 5 where exists a high degree of convergence between cutaneous, muscular, visceral afferences (this accounting for the referred pain phenomenon), and between various sensory modalities.

The main neurotransmitter involved in pain transmission at the dorsal horn level seems to be substance P. Liberation of substance P at this level has been demonstrated only after stimulations recruiting Aβ and C fibers. However, a number of neuropeptides are also present in the dorsal horn (sometimes together with substance P in the same cells) and may be involved (cholecystokinin, VIP, bombesin, somatostatin).

Ascending pathways

Most pain related fibers, are located in the anterolateral quadrant of the cord. Axons of cells in
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lamina 1 and 2 cross the midline and ascend directly to the ventral lateral complex of the thalamus (lateral part for trunk and limbs, medial part for face). These fibers form the neospinothalamic tract rather lateral in the anterolateral column. In the thalamus they converge with fibers from the medial lemniscus conveying touch and proprioceptive information. (Only 10% of neurons in the ventrobasal complex respond to noxious stimuli). All these neurons are somatotopically arranged, their axons reach the somatic sensory cortex. Neospinothalamic tract concerns discriminative aspects of pain sensation bringing informations on the location, type, and intensity of the stimulus.

Axons of the cells in lamina 5 form the so called paleospinothalamic tract or reticulospinothalamic tract, located medially in the anterolateral column (many others fibers of the same origin ascend in other sections of the cord (ventral, dorsolateral). The corresponding neurons display functional characteristics different from those of neurons belonging to the neospinothalamic system: large and diffuse receptor field, no somatotopic arrangement, no reliable coding, variability of responses...

These fibers terminate at various levels of the brain stem reticular formation up to the medial thalamic nuclei (intralaminar). At the level of bulbopontine reticular formation these fibers could mediate visceral response to pain stimuli. At the pontomesencephalic level they are probably responsible for awakening response to pain. At upper mesencephalic level a large number of fibers reach the periaqueductal gray matter. This region, and more generally the central gray surrounding ventricular walls at diencephalic and mesencephalic level, has multiple reciprocal connexions with hypothalamus, limbic system, motor and premotor cortex. It is highly likely that through these connexions are mediated important correlates of pain sensation related to emotion, memory, cognition, behavioural responses. However, the discrete anatomy of these connexions is yet virtually unknown.

Modulation of pain inputs

The transmission of pain related information in the CNS is subjected to a considerable degree of modulation occurring at the spinal level from both segmental peripheral and descending controls. In 1965, Melzack and Wall proposed that "a neural mechanism in the dorsal horn acts like a gate which can increase or decrease the flow of nerve impulses from peripheral fibers to the CNS. Somatic impulse is therefore subjected to the modulating influences of the gate before it evokes pain perception and responses... Physiological evidence suggests that the SG is one of the likely sites of the spinal gating mechanisms».

Modulation from primary afferents

Neurons of the SG are activated by inputs from large fibers A carrying touch information in their peripheral and central (dorsal column) course. The axons of these SG cells have inhibitory effects on the transmission of pain information from primary afferents to the neurons of origin of the spinothalamic tracts (the so called T cells). This inhibition is probably mainly presynaptic though postsynaptic effects are also possible. The control of pain transmission by large fibers activity explain the well documented value of the electrical stimulation of peripheral nerves and dorsal columns to relieve some clinical pain conditions.

The neuropharmacology of these inhibitory effects is not completely understood. Gaba is probably involved but the main role seems to be played by endogenous ligands (enkephalin, dynorphin) of opiate receptors. Jessel and Iversen propose a model in which encephalnergic neurons of the SG exert their inhibitory action through opiate receptors located in the presynaptic terminals of afferent pain fibers. Even though the precise mechanisms of pain modulation by opioid substances at the spinal level is not yet clear, these data have lead to the use of intrathecal morphin in certain pain conditions.

Descending controls

There is now evidence that the electrical stimulation of discrete area of the brain stem can produce strong and long lasting analgesia. The most important of these area are first at mesencephalic level the ventral and lateral part of the PAG, and at the bulbopontine level the Nucleus Raphe Magnus (NRM).

The effect of PAG stimulation are mediated through NRM and NRM in turn projects directly to the dorsal horns (lamina 1, 2, 4, 5), the NRM-spinal tract being located in the dorsolateral columns. The physiological action of this central system for analgesia is not completely understood. It could be activated from the periphery, operating as a negative feed-
back supraspinal loop, and it could as well convey the influences of rostral brain (cognitive, emotional...) on pain sensations.

The neuropharmacology of this system involves serotonin, noradrenalin and opioid substances. Serotonin is the main neurotransmitter mediating NRM effects on spinal cord. Analgesia induced by electrical stimulation of NRM can be enhanced by tryptophan derivatives, metabolic precursors of serotonin. The role of opioid substances is yet unclear: some publications claim that electrical stimulation of PAG produces high levels of endorphin in the CSF and that the analgesia effect is reversed by naloxone, but contradictory results have also been published. Nevertheless, the hypothesis that opioid mechanisms are involved in central analgesia has lead to the administration of intraventricular morphin in certain pain conditions.

Conclusion

The fine circuitry and neuropharmacology of pain related systems in the CNS are not completely unravelled. For methodological and ethical reasons the experimental research on pain remain difficult. However, considerable progress in our understanding have been achieved in the last 25 years and have lead to impressive clinical applications.

References


