Noziception, pain, and antinociception:
current concepts

Nozizeption, Schmerz und Antinozizeption

Summary The physiology of noziception involves a complex interaction of peripheral and central nervous system (CNS) structures, extending from the skin, the viscera and the musculoskeletal tissues to the cerebral cortex. The pathophysiology of chronic pain shows alterations of normal physiological pathways, giving rise to hyperalgesia or allodynia. After integration in the spinal cord, noziceptive information is transferred to thalamic structures before it reaches the somatosensory cortex. Each of these levels of the CNS contain modulatory mechanisms. The two most important systems in modulating noziception and antinociception, the N-methyl-D-aspartate (NMDA) and opioid receptor system, show a close distribution pattern in nearly all CNS regions, and activation of NMDA receptors has been found to contribute to the hyperalgesia associated with nerve injury or inflammation. Apart from substance P (SP), the major facilitory effect in noziception is exerted by glutamate as the natural activator of NMDA receptors. Stimulation of ionotropic NMDA receptors causes intraneuronal elevation of Ca²⁺ which stimulates nitric oxide synthase (NOS) and the production of nitric oxide (NO). NO as a gaseous molecule diffuses out from the neuron and by action on guanylyl cyclase, NO stimulates in neighboring neurons the formation of cGMP. Depending on the expression of cGMP-controlled ion channels in target neurons, NO may act excitatory or inhibitory. NO has been implicated in the development of hyperexcitability, resulting in hyperalgesia or allodynia, by increasing nociceptive transmitters at their central terminals. Among the three subtypes of opioid receptors, µ- and δ-receptors either inhibit or potentiate NMDA receptor-mediated events, while κ opioids antagonize NMDA receptor-mediated activity. Recently, CRH has been found to act at all levels of the neuraxis to produce analgesia. Modulation of noziception occurs at all levels of the neuraxis, thus, eliciting the multidimensional experience of pain involving sensory-discriminative, affective-motivational, cognitive and locomotor components.

Introduction

The integrity of all living organisms is guaranteed by interaction of two highly specialized systems: the immune system and by the ability of the brain to detect and remember danger. Whereas under physiological conditions the activities of the immune system never reach consciousness, pain immediately alerts the organism to the presence of damaging stimuli. Although both the immune and the nociceptive system appear to have been evolved separately, it is evident that during evolution mutual communication pathways have been developed by sharing common signal molecules and receptor mechanisms (9). Pain is usually defined as an “unpleasant sensory and emotional experience associated with actual or potential tissue damage. Pain is always subjective, each individual learns the application of the word through experiences related to injury in early life” (79). Pain is not homogeneous and comprises three categories: physiological, inflammatory, and neuropathic pain. Pain is entirely a function of cerebrocortical structures composed of discriminative, affective-motivational, cognitive and locomotor components. Acute pain is mostly short-lasting because powerful antinociceptive mechanisms are simultaneously turned on by the noxious stimulus. Chronic pain is frequently associated with degenerative tissue diseases such as rheumatoid arthritis, does not spontaneously resolve and serves no obvious useful biological function (70), and it may be that for that reason genes favoring an opposing force to chronic pain have not been developed during evolution.

Physiological pain

Physiological pain is initiated with the generation of action potentials of specialized sensory nociceptor fibers innervating peripheral tissues. The action potentials transmitting somatic pain are conducted to the CNS by forming a three-neuron chain transferring nociception to the cerebral cortex. The first-order neurons with their cell bodies in the dorsal root ganglion end in the dorsal horn of the spinal cord, the trigeminal nociceptors in the trigeminal sensory nuclei of the brainstem, and synapse there with the second-order neurons, which axons ascend in the spinothalamic tract to the thalamus. The third-order neurons project to the postcentral gyrus of the cerebral cortex, where information is somatotopically organized. Most nociceptive signals originating from visceral organs reach the CNS via afferent fibers in sympathetic nerves. Specific visceral nociceptors have been found in the heart, lungs, testes and biliary system, whereas noxious stimulation of the gastro-intestinal tract appears to be detected mainly by non-specific visceral receptors that use an intensity-encoding mechanism (23, 49). Visceral nociceptive messages are conveyed to the spinal cord by relatively few visceral afferent fibers which activate many central neurons by extensive functional divergence through polysynaptic pathways (18, 59). Impulses in visceral afferent fibers excite spinal cord neurons also driven by somatic inputs from the corresponding dermatome. Noxious intensities of visceral stimulation are needed to activate viscerosomatic neurons, most of which can also be excited by noxious stimulation of their somatic receptive fields. Thus, visceral pain is the consequence of a diffuse activation of somato-sensory nociceptive systems which prevents accurate spatial discrimination or localization of the stimuli. Although a specific ascending pathway for visceral nociception has not been found, projection of viscerosomatic neurons include the spino-reticular and spino-thalamic tracts which trigger general reactions of alertness and arousal and evoke unpleasant and poorly localized sensory experiences.

Clinical pain

Inflammatory pain is initiated by unspecific stimulation of the sensory innervation of tissues by mediators released during the interaction of the immune