Anatomy, physiology and pharmacology of pain

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Abstract

Although there is an anatomical framework that is involved in pain processing, this system is not 'hard wired' but undergoes changes affecting the sensitivity and the 'gain' of nociception. Peripheral sensitization contributes to increasing afferent barrage to the spinal cord. It is mediated by many diverse elements, including nerve and immune cells, in a complex array of algogenic products. Numerous receptors and ion channels are involved. Continuing increased input into the spinal cord causes further changes of central sensitization. The glutamate receptor, N-methyl-D-aspartate (NMDA) is pivotal to these processes. The NMDA receptor is therefore a potential target for analgesic therapy. Visceral pain shares the features of the pain mechanisms described in this article, but there are some anatomical, physiological and biochemical differences to somatic pain. Damage to nerves causes changes in excitability, which induce similar peripheral and central sensitization processes that contribute to neuropathic pain. Knowledge of all these processes identifies not only a rationale for standard pain treatments but also novel potential analgesic targets. However, these systems display complex interactions and, rather than targeting a single moiety, a multi-mechanistic approach to analgesia is required.

Keywords cytokines; nerve growth factor; neuropathic; N-methyl-D-aspartate; nociceptors; sensitization

Pain is a singular human experience influenced by diverse elements such as emotion, cognition, memory and social constructs. Although it is convenient to frame pain in anatomical, physiological and pharmacological terms, it should be considered that many other factors are involved and require a multifactorial approach to achieve analgesia (Table 1). Pain can have pathological consequences, and its control is a treatment imperative (Table 2).

Pain pathway: peripheral nociceptors to spinal cord and to brain

Specificity theory states that there is a specific pain system that transfers information about potential or actual tissue damage to the place of perception: the brain. Nociceptive energy is *transduced* into electrophysiological signals that are *transmitted* to *perceptive* apparatus. However, the pain pathway is not 'hard wired', but undergoes profound functional changes and modulation under certain conditions, such as tissue damage and inflammation (e.g. postoperative pain). This plasticity is mediated by many mechanisms, including peripheral/primary and central/secondary sensitization. The substrate for these changes is a plethora of chemical mediators peripherally and spinally, comparable in complexity to neurotransmitters in the brain.

Anatomical classification of nociceptors: specialized detectors (nociceptors) respond to noxious stimuli of many modalities, including thermal, chemical and mechanical. Somatic nociceptors have been classified according to anatomical features and physiological characteristics.

Unmyelinated C polymodal nociceptors are activated by many potentially tissue-damaging modalities, are associated with prolonged 'burning' pain, and are slowly conducting (0.5–2.0 m/s). Some may have a differential sensitivity to heat or mechanical stimuli.

Aδ, thinly myelinated, mechano-heat receptors, are thought to mediate a briefer 'sharp' pain. These larger fibres are more rapidly conducting (5–20 m/s). Aδ fibres are also delineated

Definitions

Pain
- An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such
- Has also been described in terms of a psychological and mental experience. Although seemingly trite, pain is what the patient says it is

Allodynia
- Pain due to a stimulus that does not normally provoke pain
- Clinically mechanical allodynia is tested by stroking with a brush or cotton wool or by punctuate stimuli such as with a von Frey hair. Non-noxious sensory stimuli of other modalities (e.g. heat/cold) can also be tested

Hyperalgesia
- An increased response to a stimulus that is already painful; the consequence of primary and secondary sensitization
- Mechanical hyperalgesia is assessed with von Frey hairs (of sufficient strength to provide a painful punctuate stimulus), and thermal hyperalgesia with thermotesting

Dysaesthesia
- An unpleasant abnormal sensation, whether spontaneous or evoked
- Hyperalgesia and allodynia are specific cases of dysaesthesia

Hyperaesthesia
- Increased sensitivity to stimulation, excluding the special senses
- Hyperalgesia and allodynia are specific cases of hyperaesthesia

Table 1

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Pathophysiological associations of pain

- Neurohumoral alterations at site of injury
- Alteration in synapses and nociceptive processing at the dorsal horn of the spinal cord

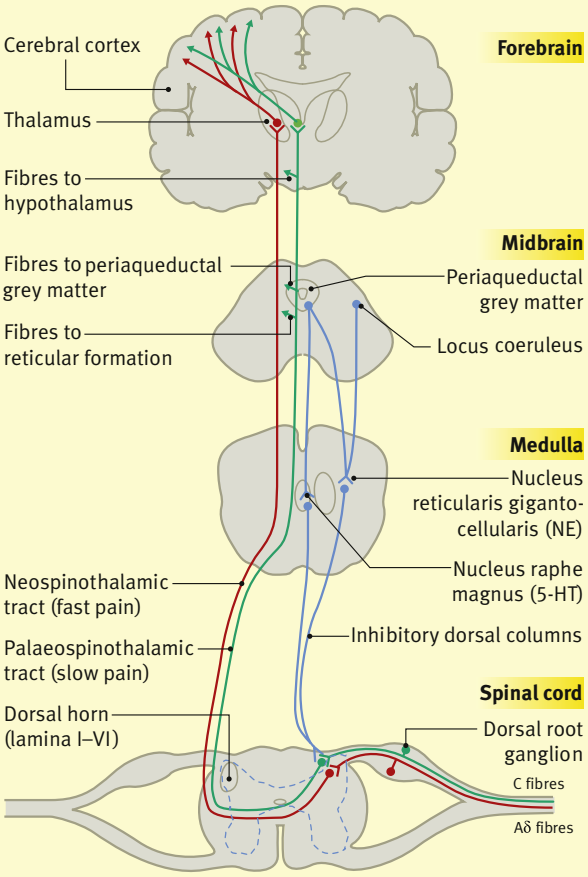
} can lead to persistent pain states

- Neuroendocrine
  increased catabolic: cortisone, glucagon, growth hormone, catecholamines
  decreased anabolic: insulin, testosterone
  increased plasminogen activator inhibitor (increased coagulation)
- Sympathoadrenal via adrenal gland and lateral horns of spinal cord

All four of the above result in the following clinical effects
CNS: inhumane, misery, anxiety, depression, sleep disturbance
Cardiovascular: increased blood pressure, heart rate and vascular resistance, increased cardiac ischaemia
Respiratory: cough inhibition (pneumonia), hyperventilation (respiratory alkalosis)
Gastrointestinal: ileus, nausea, vomiting
Genitourinary: urinary retention, uterine inhibition
Muscle: restless increased oxygen consumption, immobility and increased incidence of pulmonary thromboembolism
Metabolic: see above

Table 2

Spinal and supraspinal pathways of pain



Ascending nociceptive fast (red) and slow (green) pathways.
Descending inhibitory tracts (blue).
5-HT, 5 hydroxytryptamine; NE, norepinephrine

Figure 1

into two types, depending on their differential responsiveness to intense heat. A final group of nociceptors do not appear to exhibit sensitivity to noxious stimuli. These 'silent' nociceptors develop novel sensitivity usually after tissue injury or inflammation. Silent nociceptors have been well characterized in the visceral domain, although there is some evidence to support the existence of somatic counterparts.

Biochemical classification of nociceptors: an anatomical framework may not clearly identify therapeutic strategies. Identification of pain mechanisms has been suggested as the key to analgesia. To whit, nociceptors can be classified by biochemical properties. Particular nociceptors express proteins such as substance P and calcitonin gene-related peptide (CGRP) and are dependent on nerve growth factor (NGF) for development. They synapse in the more superficial laminae of the superficial dorsal horn (I, and II outer) whilst the non-protein expressing nociceptors synapse with their second-order neurons in lamina II inner. It has been postulated that the protein-expressing nociceptors are more important in inflammatory pains and the non-protein-expressing are pivotal to neuropathic pain states. Nociceptors also synapse in the deeper laminae such as V and X, and these project to separate brain areas.

Spinal cord to brain: secondary afferents decussate and pass up the spinal cord to the midbrain via the spinothalamic, spinoreticular and spinomesencephalic tracts to the thalamus and to sensory cortex, but also have many other links, such as to reticular formations, limbic and hippocampal areas (Figure 1). The different pathways may have functional correlates involving memory, cognition and emotion, which contribute to the neural network of overall pain perception. Moreover, neurons that project from these areas of the brain provide descending modulation of spinal cord processing.

Pain modulation

Primary/peripheral sensitization

Elements of peripheral sensitization – the threshold for activation of nociceptors is not fixed and they exhibit activity-dependent changes. This plasticity is manifest as peripheral sensitization. Increases in pain sensitivity are mediated by the local release of chemical mediators ('inflammatory soup') from the primary sensory nerve terminal and a collection of diverse non-neuronal cells, including fibroblasts and immune cells. These mediators stimulate/activate the nociceptor directly (e.g. hydrogen ions, ATP and 5 hydroxytryptamine (5-HT)) or by increasing