

## Physiology of Pain

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### Summary

Understanding pain physiology is very important in countering it. From what is known it is clear that pain perception involves transduction, transmission, and modulation. Both facilitators and inhibitors are involved. The body response to painful stimuli may be helpful or counter-productive. Better knowledge allows both artificial modulation of pain and suppression of harmful reflex responses

### INTRODUCTION

Pain is defined by the International Association for the Study of Pain (IASP) as 'an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage'. Pain has objective, physiological sensory aspects as well as subjective, emotional and psychological components. The term 'nociception' is used only to describe the neural response to traumatic or noxious stimuli.

### PERIPHERAL TRANSMISSION

Even though transmission occurs from the peripheral receptor to the brain as one continuous process, for convenience this section is divided into peripheral and central transmission.

Peripheral transmission of pain consists of production of electrical signals at pain nerve endings (transduction) followed by propagation of those signals through the peripheral nervous system (transmission).

### Transduction

The primary sensory structure that accomplishes transduction is the nociceptor. Most nociceptors are free nerve endings that sense heat, mechanical and chemical tissue damage. Several types are described:

1. *mechanoreceptors*, which respond to pinch and pinprick,
2. *silent nociceptors* which respond only in the presence of inflammation, and
3. *polymodal mechano-heat nociceptors*. These are most prevalent and respond to excessive pressure, extremes of temperatures ( $>42^{\circ}\text{C}$  and  $<18^{\circ}\text{C}$ ), and algogens (pain producing substances). Polymodal nociceptors are slow to adapt to strong pressure and display heat sensitization.

Vanillins are a group of compounds, including capsaicins, that cause pain. An ion channel activated directly by vanilloid compounds including capsaicin (TRPV1, previously known as VR1) has been found to

be selectively overexpressed in some small to medium diameter nociceptive neurons.<sup>1</sup> The TRPV1 receptors not only respond to pain but also to protons and to temperatures  $>43^{\circ}\text{C}$ . There are multiple TRPV1 splice variants.<sup>1</sup>

### Transmission

Pain impulses are transmitted by two fibre systems. The presence of two pain pathways explains the existence of two components of pain: fast, sharp and well localized sensation ('first' pain) which is conducted by A $\delta$  fibres, while a duller slower onset and often poorly localized sensation ('second pain') is conducted by C fibres. A $\delta$  fibres are myelinated, 2-5mcm in diameter and conduct at rates of 12 to 30m.s<sup>-1</sup>, whereas C fibres are unmyelinated, 0.4-1.2mcm in diameter and conduct at rates of 0.5 to 2m.s<sup>-1</sup>. Both fibre groups end in the dorsal horn of the spinal cord. A $\delta$  fibres predominantly terminate on neurons in lamina I of the dorsal horn, whereas the dorsal root C fibres terminate in laminae II and III. The synaptic junctions between these first order neurons and the dorsal horn cells in the spinal cord are sites of considerable plasticity (i.e. the synaptic connections demonstrate the ability to change the strength of their relationship). For this reason the dorsal horn has been called a gate, where pain impulses can be modified (or 'gated').

Second-order neurons are either nociceptive-specific or wide dynamic range (WDR) neurons. Nociceptive-specific neurons serve only noxious stimuli and are arranged somatotopically in lamina I of the dorsal horn of the spinal cord. This means that they have a discrete somatic receptive field and are spatially arranged in the central nervous system according to the part of the body that they innervate. They are normally silent and respond only to high threshold noxious stimuli. WDR neurons receive both noxious and non-noxious afferent input from A $\beta$ , A $\delta$  and C fibres. Differentiation between noxious and innocuous stimuli occurs by a higher frequency of WDR neuron discharge to noxious stimuli. WDR neurons are most abundant in lamina V.

### CENTRAL TRANSMISSION

Central transmission includes transmission and

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perception whereby the electrical signals are transmitted from the spinal cord to the brain.

### Transmission

The axons of most of the second order neurons cross the midline at the anterior commissure to the contralateral side of the spinal cord, and ascend as the spinothalamic tract. This tract ends in the thalamus, reticular formation, nucleus raphe magnus and the periaqueductal grey and can be divided into lateral and medial parts. The lateral spinothalamic (neospinothalamic) tract projects mainly to the ventral posterolateral nucleus of the thalamus and carries discriminative aspects of pain, such as location, intensity, and duration of pain. The medial spinothalamic (paleospinothalamic) tract projects to the medial thalamus and is responsible for mediating the autonomic and unpleasant emotional perception of pain.

### Perception

The third order neurons project from the thalamus to somatosensory areas I and II in the post-central gyrus and superior wall of the sylvian fissure. Perception and discrete localization of pain take place in these cortical areas. Some fibres project to the anterior cingulate gyrus and are likely to mediate the suffering and emotional components of pain.

### MODULATION

Modulation of pain occurs peripherally at the nociceptor, in the spinal cord, or in supraspinal structures. This modulation can either inhibit or facilitate pain.

#### Peripheral modulation

Nociceptors and their neurons display sensitization following repeated stimulation. Sensitization of nociceptors results in a decrease in threshold, an increase in frequency response, a decrease in response latency and spontaneous firing, even after cessation of the stimulus ('after discharges'). This primary hyperalgesia (increased sensitivity to pain) is mediated by release of algogens like histamine, bradykinin, PGE<sub>2</sub> and leukotrienes from damaged tissues.

Secondary hyperalgesia or neurogenic inflammation is manifested by the triple response of flare, local oedema and sensitization to noxious stimuli. It is primarily due to antidromic release of substance P from collateral axons of primary afferent neurons. Substance P degranulates histamine and serotonin, vasodilates blood vessels, causes tissue oedema and induces formation of leukotrienes.

#### Central modulation

Modulation can either facilitate or inhibit pain. The mechanisms for facilitation are:

1. Windup and sensitization of second order neurons
2. Receptive field expansion
3. Hyperexcitability of flexion responses.

Neurochemical mediators of central sensitization include substance P, CGRP (calcitonin gene related peptide), VIP (vasointestinal peptide), cholecystokinin, angiotensin, galanin, L-glutamate and L-aspartate. These substances trigger changes in membrane excitability by

interacting with G-protein coupled receptors, activating intracellular second messengers, which in turn phosphorylate substrate proteins. A common pathway leads to increased intracellular calcium concentration. For example glutamate and aspartate activate the NMDA receptor. Stimulation of ionotropic NMDA receptors causes intraneuronal elevation of Ca<sup>2+</sup>, 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 the formation of cGMP in neighbouring neurons. Depending on the expression of cGMP-controlled ion channels in target neurons, NO may be excitatory or inhibitory. NO has been implicated in the development of hyperexcitability, resulting in hyperalgesia or allodynia (a painful response to a usually non-painful stimulus), by increasing nociceptive transmitters at their central terminals.

### Inhibitory mechanisms

Inhibitory mechanisms can be either segmental or supraspinal.

*Segmental inhibition* consists of activation of large afferent fibres subserving epicritic sensation, inhibitory WDR neurones and spinothalamic activity. Glycine and  $\gamma$ -amino butyric acid (GABA) are amino acids that function as inhibitory neurotransmitters. Segmental inhibition appears to be mediated by GABA-B receptor activity, which increases K<sup>+</sup> conductance across the cell membrane.

*Supraspinal inhibition* occurs whereby several supraspinal structures send fibres down the spinal cord to inhibit pain at the level of the dorsal horn. These include periaqueductal grey, reticular formation, and nucleus raphe magnus (NRM). Axons from these structures act pre-synaptically on the primary afferent neurons and post-synaptically on second-order neurons (or interneurons). These inhibitory pathways utilise monoamines, such as norepinephrine and serotonin, as neurotransmitters and terminate on nociceptive neurons in the spinal cord as well as on spinal inhibitory interneurons which store and release opioids. Norepinephrine mediates this action through  $\alpha_2$  receptors. The endogenous opiate system act via enkephalins and  $\beta$ -endorphins. These mainly act presynaptically whereas the exogenous opiates act postsynaptically.

### REFLEX RESPONSES

Somatic and visceral pain fibres are fully integrated with the skeletal motor and sympathetic systems in the spinal cord, brain stem and higher centers. These synapses are responsible for reflex muscle activity that is associated with pain. In a similar fashion reflex sympathetic activation causes the release of catecholamines, locally and from the adrenal medulla. This increases heart rate and blood pressure with a consequent increase in myocardial work, increased metabolic rate and oxygen consumption. Gastrointestinal tone is decreased leading to delayed gastric emptying.

Pain also causes an increase in the secretion of catabolic hormones and decreased secretion of anabolic hormones. The metabolic responses to pain include hyperglycaemia due to gluconeogenesis and decreases in insulin secretion or action increased protein metabolism and increased lipolysis. The respiratory responses could be either hyperventilation due to stimulation of respiratory center or hypoventilation due to splinting and reflex muscle spasm. The diencephalic and cortical

responses may include anxiety and fear. Pain stimulates psychological mechanisms with deleterious emotional effects.

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