



## PHYSIOLOGY OF PAIN

Dr.K.Venugopal, Dr.M.Swamy FRCA  
Darlington Memorial Hospital, UK

### Self Assessment

**Before reading the tutorial, please answer the following questions. Answers are found in the text.**

1. The following are true with regards to transduction:
  - a) It is production of electrical signals at the pain nerve endings.
  - b) Mechanoreceptors are most prevalent.
  - c) Most nociceptors are free nerve endings.
  - d) Silent nociceptors do not respond to any stimulus
  - e) Nociceptors display adaptation and sensitization
2. A $\delta$  fibres:
  - a) Carry fast pain
  - b) Terminate predominantly in lamina II
  - c) Are unmyelinated
  - d) Conduct at rates 12 to 30 m/s
  - e) Also carry non-noxious afferent input.
3. Second order neurons carrying pain information:
  - a) Cross midline anterior to central canal
  - b) Spinothalamic tract end only in the thalamus
  - c) Ipsilateral pain sensation is lost in spinal cord hemi section
  - d) Lateral spinothalamic tract carries discriminative aspect of pain
  - e) Are all myelinated
4. With regards to modulation of pain:
  - a) It begins at the dorsal horn of spinal cord
  - b) It is either inhibitory or facilitatory
  - c) Common pathway involves intracellular calcium concentration
  - d) Enkephalins act post synaptically
  - e)  $\beta$ -endorphins act presynaptically
5. The reflex responses to pain include:

- a) Increase in myocardial work
- b) Urinary incontinence
- c) Decrease in testosterone
- d) Hyperglycaemia
- e) Increase in fibrinolysis

## *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.” Thus pain has objective, physiologic sensory aspects as well as subjective emotional and psychological components. The term “**nociception**” (Latin – noci = harm or injury) is used only to describe the neural response to traumatic or noxious stimuli.

### *Peripheral Transmission*

Peripheral transmission of pain consists production of electrical signals at the 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 mechanoheat nociceptors. The last are most prevalent and respond to excessive pressure, extremes of temperatures ( $>42\text{ }^{\circ}\text{C}$  and  $< 18\text{ }^{\circ}\text{C}$ ), and algogens (pain producing substances). Polymodal nociceptors are slow to adapt to strong pressure and display heat sensitization.

Recently, vanilloid receptor-1 (VR-1) was isolated from the sensory neurons. Vanillins are a group of compounds, including capsaicins that cause pain. The VR1 receptors not only respond to pain but also to protons and to temperatures  $>43\text{ }^{\circ}\text{C}$ . Another receptor, VRL-1, which responds to temperatures above  $50\text{ }^{\circ}\text{C}$  but not to capsaicin, has been isolated from C fibres.

#### **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; and a duller slower onset and often poorly localized sensation (second pain) which is conducted by C fibres.  $A\delta$  fibres are myelinated,  $2 - 5\text{ }\mu\text{m}$  in diameter and conduct at rates of  $12 - 30\text{ m/s}$ , whereas C fibres

are unmyelinated, 0.4 – 1.2  $\mu\text{m}$  in diameter and conduct at rates of 0.5 to 2 m/s. Both fibre groups end in the dorsal horn of the spinal cord. A $\delta$  fibres terminate predominantly on neurons in laminae I and V, whereas the dorsal root C fibres terminate in laminae I and II. The synaptic junctions between these first order neurons and the dorsal horn cells in the spinal cord are sites of considerable plasticity. For this reason the dorsal horn has been called a gate, where pain impulses can be “gated” i.e., modified.

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 and have a discrete somatic receptive field; 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 perception** whereby the electrical signals are transmitted from the spinal cord to the brain. Even though the transmission occurs from the peripheral receptor to the brain as one continuous process, for convenience we have divided this into peripheral and central transmission

### *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 to ascend as the spinothalamic tract ending in the thalamus, reticular formation, nucleus raphe magnus and the periaqueductal gray. This ascending tract can be divided into lateral and medial. 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. 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 are located in the thalamus and project to somatosensory areas II and I 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 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 edema and sensitization to noxious stimuli. It is primarily due to antidromic release of substance P (sP) from collateral axons of primary afferent neurons. Substance P degranulates histamine and serotonin, vasodilates blood vessels, causes tissue edema and induces formation of leukotrienes.

### **Central modulation**

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

- a) Windup and sensitization of second order neurons.
- b) Receptive field expansion
- c) Hyper excitability of flexion responses.

Neurochemical mediators of central sensitization include sP, CGRP, VIP, 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, by increasing nociceptive transmitters at their central terminals.

### **Inhibitory mechanisms can be either Segmental or Supraspinal.**

Segmental inhibition consists of activation of large afferent fibres subserving epicritic sensation inhibitory WDR neuron 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<sub>B</sub> 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 gray, 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 noradrenaline 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. Noradrenaline 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 hyperglycemia 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.

## Summary

Understanding pain physiology is very important in countering it. From what is known it is clear that pain recognition involves transduction, transmission, modulation and perception. The signal is modulated at various levels before perceived. Various transmitters, facilitators and inhibitors are involved. Body responds to painful stimuli, which may be helpful or counter-productive. Better knowledge helps not only in artificial modulation of pain but also to suppress the harmful reflex responses.

## References

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2. Carl C Hug, Jr In: Pain Management (Clinical Anaesthesiology Third Edition) Lange/McGraw-Hill 2002, 309 – 344