

PHYSIOLOGY OF PAIN – GENERAL MECHANISMS AND INDIVIDUAL DIFFERENCES

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ABSTRACT. The current article aims at reviewing the general mechanisms of painful sensation, enlisting painful stimuli, common and special types of pain, and also the three stages of pain occurrence. The emphasis is on pain modulation, by gate control, and also by means of wind-up, temporal summation and central hyper-sensitization. A closer look at the way pain is perceived by children and elderly, and men and women as well as makes the object of the present paper, which includes new findings in the field.

Keywords: nociception, pain induction, perception, integration, gate control theory, first and secondary pain, sensitization, psychological modulation, age- and sex-related differences

INTRODUCTION

What is pain? Pain is an unpleasant sensation that the brain interprets after a peripheral lesion of nociceptive intensity. Pain is more than just a physiological event. It's a dynamic process that challenges a continuous interaction between complex systems. Pain perception can be modulated or adjusted according to the emotional behavior of the subject – focusing on the pain leads to higher pain intensity, while positive thinking relieves some of the pain. Also, in certain cases (such as chronic back pain), physical exercise contributes to an increase of pain tolerance (and a decrease of anxiety/depression that often goes with the pain). Pain decreases when sweet fragrances are perceived or during exercises such as meditation or hypnosis.

There are different **types of pain**:

- First/fast pain (localized, acute, that appears in 0.1 seconds after the painful stimulus and ends with its action), accompanied by a flexion reflex and it is a consequence of the stimulation of A-delta myelinated fibers.
- Secondary pain – slow, chronic, diffuse, that persists longer than the

stimulus; it is accompanied by reflex muscular contraction and it is a result of unmyelinated C fibers.

Nociception is the conscious perception of pain that has mechanical, thermal or chemical origin. Nociceptors are peripheral receptors. They represent the end segment of the unmyelinated and myelinated dendrites of sensitive neurons that make a cutaneous nerve. They have a very high excitability threshold.

The nociceptive information can be inhibited by stimulation of the opioid receptors found at presynaptic level in primary afferent neurons. The sensory signals that enter at spinal cord level inhibit the nociceptive signals through a non-opioid gate mechanism. The descendant systems also modulate the pain sensitivity in the spinal cord. Acute stress can lead to analgesia by means of an opioid mechanism, as well as by a non-opioid mechanism. The pain sensitivity control is influenced by learning (bio-feedback techniques and social factors) and can be altered in depression, manic disorders and schizophrenia.

There are a number of stimuli that can determine a painful sensation:

Type of stimulus	Example
Mechanical	Pressure, vibration, traction of internal organs
Thermal	Temperature higher than 45°C
Chemical	Amines, peptides, hypoxia, prostaglandins

The birth of pain and its perception happen during a series of three **STAGES**:

1. Peripheral stage – peripheral tissue sensitization
2. Transmission stage – by specialized structures
3. Integration of pain – can be conscious or not and involves functions such as: attention, concentration, memory, affect.

The **PERIPHERAL STAGE** involves tissue damage due to mechanical, thermal or chemical stimuli, followed by a release of pain-inducing substances and stimulation of the nociceptors. Some of these substances include: **amines** (serotonin and noradrenaline – descendant modulation of pain, histamine – itch sensation), **endogenous opioid peptides** (enkephalins, beta-endorphins, dinorphins – endogenous agonists for opioid receptors that exhibit an inhibitory response), **amino acids** (acetylcholine – rapid transmission of pain, glutamate – hyperalgesia, GABA – inhibitory response), **neuropeptides** (NGF and CGRP – central and peripheral action), **kinins** (tachykinins – slow transmission of pain, substance P – induces inflammation signs, bradykinin – also induces prostaglandin release), **prostaglandins** (E, F – amplify the effect of serotonin and kinins) and **metabolites** (lactic acid, ATP, ADP, K⁺ - a decrease of pH has a nociceptive effect by opening the proton activated ion channels).

At peripheral level, the noxious stimuli activate polymodal receptors innervated by C-fibers. When inflammation occurs, the fibers are subdued to chemical aggression. In the affected tissues, chemical substances, such as bradykinin, substance P, CGRP are released. They constitute the so-called “inflammatory soup”. The consequence is a sensitization of

nerve endings that leads to pain, edema and an increase in local temperature. Pain starts to be perceived at a pH of 6.2 and reaches a maximum at 3.2.

The **TRANSMISSION STAGE** involves the following: peripheral receptors, nervous tracts, spinal mechanisms, ascending and descending pathways, the brainstem, thalamus and the cortex.

In 1965, Melzack and Wall published the well-known gate **control theory** of pain. According to this theory, a mechanism in the brain acts as a gate to increase or decrease the flow of nerve impulses from the peripheral fibers to the central nervous system. An “open” gate permits the flow of nerve impulses, and as a result, the brain is able to perceive pain. A “closed” gate doesn't permit flow of nerve impulses, decreasing the perception of pain. This theory has been widely accepted, but it leaves unanswered questions, such as chronic pain issues, sex-based differences and the effects of previous pain experiences. Thus, in 1999, Melzack and Wall came up a newer theory of pain that answered some of these questions. This “new” theory, the **neuromatrix theory**, stipulates that every human being has an innate network of neurons that they named the “body-self neuromatrix.” Each person’s matrix of neurons is unique and is affected by all facets of the person’s physical, psychological, and cognitive traits, and also by their experience.

In pain transmission in the dorsal horn, the neurotransmitters are released after the activation of afferent fibers of neurons that are localized in the posterior horn. The Rolando gelatinous substance is one of the most dense reception areas. A number of substances exhibit a stimulating or an inhibitory response at the dorsal horn level:

Stimulant	Inhibitory
Substance P	Enkephalins
CGRP	Somatostatin
Glutamate	Noradrenaline
Nitric oxide	Serotonin
Aspartate	GABA

Phenomenon that influence pain transmission:

1. Wind-up phenomenon – a progressive increase of the duration and amplitude of the action potentials in the neurons of the dorsal horn after a repetitive and constant stimulation of C fibers. It is responsible of secondary pain.

2. Temporal summation – a physical and mental correlation of the amplification phenomenon due to the stimulation of the high threshold C or A δ fibers. Clinically, this leads to hyperalgesia or secondary pain.

3. Central hypersensitivation – it is the pathophysiological mechanism of chronic pain.

The **INTEGRATION STAGE** involves structures such as: the brainstem, the thalamus, hypothalamus, subcortical nuclei and the brain cortex. These are responsible of: flexion reflexes, immune, endocrine, respiratory, vegetative responses, pain sensation and its perception, affective and behavioral reactions, pain learning and memory. The pain control depends on the gate system and on the thalamus. The areas that become activated during simple nociception are: the somatosensory cortex (S1, S2), the anterior cingulate cortex and the insular cortex.

SPECIAL TYPES OF PAIN

Neuropathic Pain

Chronic pain, due to injury to the peripheral nerves, is known as neuropathic pain. This pain is paradoxical. Injury to the peripheral nerves can determine sudden numbness, pain with movement, sensitivity of a partly denervated region of the body, as well as pain with electrical character, burning or tingling.

Abnormally amplified signals in the central nervous system, due to the windup phenomenon, determine central sensitization, which is translated into a higher sensitivity of spinal neurons. Central sensitization causes allodynia (eg. pain from touch) and hyperalgesia (an amplified pain response to a painful stimulus).

Phantom Pain

Approximately 70% of amputees complain of phantom limb pain, mostly during the first week that follows amputation. The patients describe the pain as stabbing, squeezing, burning and throbbing. Sometimes, the missing limb feels twisted or the patient perceives muscular cramps. Remains uncertain the exact cause of this type of pain. Some researchers think that the pain is in the central nervous system and may be due to some sort of complex somatosensory “memory”.

DIFFERENCES IN POPULATIONS

Sex-Based Differences

Women report more painful events than men do and they seem to have lower thresholds and tolerance to painful stimuli. There are also differences in the types of pain that occur more frequently in women compared to men. For instance, headaches occur in both men and women, but women experience more migraines with aura, whereas men report more migraines without aura.

The base for these differences is not very well understood. Potential mechanisms in pain include: sex hormones, differences in the brain and spinal cord, genetics, stress. Researchers have discovered that brain activity in men and women differs during a painful experience. Silverman et al used PET to observe brain activation patterns in healthy men and women who were not in pain and compared to those of men and women experiencing pain. The brain patterns of the men and women experiencing pain were significantly distinct, but there were no sex-based differences in the control group. This suggests that men and women process pain in a very different manner.

Age-based Differences

Pain in children

In the past, it was thought that children don't experience pain. Studies now indicate not only that children experience pain, but that the painful experience may have long-

lasting consequences. Research shows that the lack of analgesia for pain determines a “rewiring” of the nerve pathways involved in the transmission of pain. This means that an infant or child who experiences pain once will have an increased perception of pain during later painful events. For example, Taddio et al discovered that babies that didn't benefit from analgesia during circumcision had psychological troubles during immunization. Also, an inadequate analgesia in children after surgical interventions can increase morbidity (Anand and Hickey).

Pain in the elderly

When compared with younger adults, elderly experience more secondary pain. Thus, older adults will probably describe pain as a burn-like sensation, rather than a sharp pain. Another finding in the elderly is a delayed response time to pain. There is no proof to suggest that the intensity of pain decreases with age. Modified reactions to pain may occur because of impaired communications skills or cognitive function. In the elderly, referred pain may not respect a typical pattern, as in silent myocardial infarction. Although this difference in pain perception translates into a clinical issue, there is no final evidence to support a link between old age and silent myocardial infarction.

CONCLUSION

Never before such efforts to understand and alleviate pain have been made. Still, new areas of research include the metamorphosis of acute pain into chronic pain, placebo effect in pain, as well as psychological modulation of pain. Neurobiology promises to unravel some of the mysteries of pain at a cellular level. All these attempts will help us understand pain, this constant companion of humanity, both a faithful friend and a dreaded enemy.

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